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AORTIC THROMBOSIS

BY

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[WITH SPECIAL PLATE]

Aortic thrombosis (Leriche's syndrome) is generally considered to be a rare condition. The true incidence may be roughly assessed from post-mortem findings, and there are reports of several large necropsy series in the literature. Straus *et al.* (1946), combining the results from several such series, arrived at an incidence of 0.12%, a figure frequently quoted subsequently. Other figures are given in the Table:

Authors	No. of Cases	No. of Necropsies
Gross and Philips (1940)	7	5,350
Greenfield (1943)	24	16,935
Barnett, Moorman, and Merrick (1952)	10	4,394
Siegel and Garvin (1941)	9	6,547

Combining these figures produces 50 cases in 33,226 necropsies—an incidence of 0.15%, agreeing quite closely with the figure quoted by Straus *et al.*

Turning now to cases diagnosed clinically, Milanés *et al.* (1950, 1952) saw 30 such patients out of 4,560 referred to a special vascular clinic. The incidence of 0.61% is naturally higher than that found at necropsies on general hospital patients.

During a period of four years 32 patients with aortic thrombosis have been seen in the Diagnostic Radiological Department of St. Mary's Hospital, which has a large and very active unit specializing in the surgery of peripheral vascular disease and draws patients from all over the country. In all our 32 patients the diagnosis was confirmed by aortography, and the subsequent report is concerned with some of the findings in these patients, and in particular with the radiological findings. In addition to the cases of aortic thrombosis investigated by us, others have been referred to St. Mary's Hospital Surgical Unit after investigation and aortography at other hospitals, but these cases are not included in the present report.

Sex Incidence

There were 24 male and 8 female patients in the series. This sex difference has been observed previously and corresponds to the greater incidence of arterial disease in the male in sites other than the aorta. The reported proportions between male and female vary in different series, as they are bound to do when figures are small. Milanés *et al.* (1952) had five females among their 30 patients. These Cuban workers also claim four to one preponderance of whites as compared with negroes. Theis (1952) found 13 women among 29 patients, the highest proportion of females yet reported. The numbers of well-authenticated reports on single female cases is too great to mention here individually; those of Gough (1935), Horwitz (1948), and Brock (1953) are of particular interest and will be referred to later. There is therefore no justification for the statement made by Goodwin and Petrie (1951) that all indubitable cases reported to that date had been in males. It is hoped to show, however, that taken as a group there are differences in the aetiological factors between the female and male groups.

Age Distribution

The youngest patient in our series was 37 years when first seen here, the oldest 78 years. The average age for the whole series was 51.3 years. The age distribution is shown in the diagram (Fig. A). It will be seen that there is a fairly even distribution up to the age of 65 years; the single patient aged 78 years slightly exaggerates the average age of the series.

Aortic thrombosis has been reported at all ages. Cases have even been recorded in infancy and childhood, but these should probably be considered as a separate group, because they differ in aetiology. In 1935 Rothstein reported the case

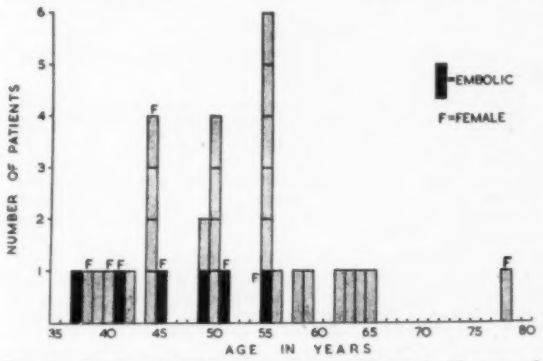

FIG. A.—Diagram showing age and sex incidence in 32 cases of aortic thrombosis. Cases considered to follow embolus in mitral stenosis are in black.

of a mongol boy who died on the 13th day after birth. At necropsy the aorta was found to be occluded. The cause was thought to have been umbilical sepsis. The paper contains a review of childhood cases to that date, all derived from necropsy records; 12 patients between the ages of 2 weeks and 12 years are described. All the cases seem to have been associated with some form of sepsis, though one case occurred during the course of diphtheria and one was superimposed on syphilitic mesaortitis. More recent reports on this condition in infants are by Morison (1945) and by Marks and Fehler (1953). Morison reported necropsy findings in three infants. In one aortic thrombosis was associated with a peculiar form of arteritis; the second infant, with an aneurysm of the ductus arteriosus, showed thrombosis of the thoracic aorta only; while in the third the renal arteries were occluded. The patient reported by Marks and Fehler was an 11-months-old boy who died during the course of an upper respiratory infection and was found to have developed a thrombosed aorta. While in some of these infants cyanosis and gangrene of lower limbs was prominent,

it was not invariable, and in some arterial disease was unsuspected until necropsy. The papers mentioned here do not constitute an exhaustive review of the subject, but are quoted to draw attention to a little-known aspect of the problem. A case of aortic thrombosis complicating syphilitic aortitis and occurring in a 20-year-old female is recorded by Gough (1935).

At the other extreme of age Pinkerton (1948) reported a case of aortic thrombosis in a man aged 81.

Theis (1952) found the average age in 19 men as 55, and in 13 women as 56 years. De Wolfe *et al.* (1954) found the average age of 47 patients with aortic or iliac thrombosis to be 54.4 years, and Beaconsfield and Kunlin (1953) 52 years in 35 patients. DeBakey *et al.* (1954) try to distinguish between patients with complete and incomplete thrombosis; they found those with complete thrombosis to be somewhat younger. The significance of this at first sight rather paradoxical finding is not certain. It is clear that aortic thrombosis is not a disease of senility, but, on the contrary, is commonest in the middle period of life, an age before degenerative changes have reached their height. The aetiology of the more common adult cases is quite different from that of the rarer childhood cases already mentioned. In adults sepsis is of no importance and atheroma is the predominant cause. Aetiology is further discussed below.

Onset of Symptoms

In 20 of our patients the onset of symptoms was very gradual—that is, the patients had difficulty in dating the onset. Twelve patients experienced a more rapid beginning of their symptoms and could date the origin more definitely. The established picture of aortic occlusion, whether embolic or thrombotic in origin, is the same, however, and these patients will be discussed together as regards symptomatology.

Relation to Trauma

In three patients in the present series the onset of symptoms may have been related to trauma.

Case 1.—Man aged 44. Received a crushing injury to the abdomen when he was trapped between two lorries. He was admitted to hospital and kept in bed for several days. Two weeks after the injury he began to complain of intermittent claudication in the right calf. This spread to involve both legs and thighs and left buttock. An aortogram showed occlusion of the aorta from the level of the second lumbar vertebra to the bifurcation of the common iliac arteries.

Case 2.—A 58-year-old man involved in a car accident. Exact details of the extent of his injuries are not now available, but they necessitated a stay in bed of nine days. On getting up he complained of intermittent claudication in both legs. Aortography revealed the presence of aortic occlusion.

Case 3.—A Pole, now aged 63, received an injury to his left leg, resulting in a fracture of the left tibia and fibula, in 1948. When he resumed walking he began to experience intermittent claudication in that leg. In 1954 he spent several weeks in hospital, suffering from jaundice (probably infective hepatitis). On his discharge from hospital intermittent claudication rapidly spread to involve the whole of the left lower extremity, left buttock, and right leg. An aortogram showed occlusion of the lower abdominal aorta.

Symptoms and Signs

Intermittent Claudication

Intermittent claudication was the outstanding symptom in the cases here described. It was present in nearly all, and consisted of an aching or burning sensation brought on by exercise and relieved within a few minutes by rest. In the early stages the pain would involve the calf muscles of one leg, beginning after the patient had walked several hundred yards. Gradually the claudication distance becomes less, and the pain comes to involve the opposite calf, thighs, and sometimes hips. The full development of this symptom may take years. Eventually the patient's walking distance may be reduced to 10–15 yards (9–14 m.), and many patients have expressed embarrassment at having to stop frequently when in the street; many will pretend to look at a shop window while resting. Some patients, however, can continue to walk for considerable distances, provided they do so slowly enough. Most patients find it impossible to continue walking when the pain has reached a certain intensity, and it may then be accompanied by marked weakness. Occasionally a patient may force himself to carry on; pins and needles in the calves may then be added to the pain. The time of rest needed before pain abates becomes progressively longer, and eventually aching may persist even at rest.

Pain occurring in addition at rest was complained of by six patients only. The only patient without intermittent claudication had suffered an attack of severe paralytic poliomyelitis many years previously and was unable to walk. His complaint was continuous pain in both legs. In a few patients the distribution of the claudication pain differed from that described above and involved mainly the buttocks or was apparently situated in the hip. However, it maintained its relation to exercise and its aching or burning characteristics. Rarely pain may be replaced by tingling and weakness caused by exercise.

We have found intermittent claudication to be the most reliable symptom of arterial insufficiency. It is our experience that where requests were received for the performance of arteriography and a history of true intermittent claudication was not obtained, the arteriograms usually showed a normal arterial tree. Conversely, claudication pain may be misdiagnosed as due to other causes.

Loss of Power and Muscle Wasting

Loss of power in the legs, frequently accompanied by muscle wasting (see below), appeared to be the symptom next in frequency, and occurred in about half the cases referred to us. The loss of power and the wasting may at times be very severe. Occasionally wasting was more marked on one side than the other. Weakness and global atrophy of legs, thighs, and buttocks were features particularly stressed by Leriche (1940), who also pointed out the ease with which these patients became fatigued. Loss of power, fatigability, and wasting are presumably related directly to the impoverished blood supply to the limbs. Another possible factor, however, is ischaemic neuropathy. Burt *et al.* (1952) have observed wasting, fasciculation, and stocking anaesthesia in their patients, and regard these as a result of ischaemic neuritis. Good evidence for the occurrence of such lesions is advanced in the papers by Edwards (1952) and Edwards and LeMay (1955). However, in one of our patients with very severe wasting the sciatic and sural nerves, examined histologically after death, showed no abnormalities.

Impotence

Leriche (1940) also stressed the diagnostic significance of impotence in the male. He accurately described this as "failure of maintained erection." Seligman (1954) described one patient said to be suffering from loss of libido. This seems unusual, and one wonders whether there was in fact some confusion in terminology. Of the present patients, four males admitted to impotence; in one 64-year-old man it appears to have been temporary, beginning two years after the first onset of symptoms, lasting six months, and clearing up without treatment. It may be presumed with some confidence that the true incidence was actually higher than this, because, unfortunately, several patients were not directly questioned regarding this symptom, and because, even when approached tactfully, men are more likely to deny than admit such a deeply distressing inability. A similar incidence has been found in other series. Beaconsfield and Kunlin (1953) saw six men with impotence in a series of 35 patients. This symptom is not confined to aortic thrombosis; it has also been observed in thrombosis of the common iliac artery. Shapiro (1952), Covey (1955), and others have reported such cases. It is accepted that operative treatment may bring about a cure of this symptom in some patients. Milanés *et al.* (1950) and Ortner and Griswold (1950) observed this after lumbar sympathectomy, and Oudot and Beaconsfield (1953) and DeBakey *et al.* (1954) after treat-

ment by arterial grafting. As stated above, however, spontaneous cure of the symptom may also occur, and the significance of operation in sometimes relieving it is not yet clear. The pathogenesis of impotence in aortic thrombosis is of some interest and will be discussed later.

Other Symptoms and Signs

Of the eight women in the series, menstruation was normal in four and four were post-menopausal. We have not observed disturbances of micturition or of bowel function. This has been reported in only one case, the patient of Tocker and Cauble (1956). She suffered from urinary incontinence, which was relieved following operation on the aorta. Since she also had a cystocele it is difficult to assess this case.

Persistent central backache is a fairly frequent complaint, though again its exact incidence cannot be assessed in the present series. In Leriche's view it was due to the intense periarteritis found in relation to the thrombosed segment of aorta. He claimed that resection of the occluded aorta relieved this symptom. We have not had an opportunity to confirm or deny this claim.

The diminished blood supply to the legs resulted almost invariably in marked coldness of the feet. Usually the patients or their spouses were very conscious of this. Exceptions were those patients who had had previous lumbar sympathectomy. While this operation does not seem to make any difference to the patient's progress, it does in many cases result in a warmer skin. Other, minor, results of the impoverished blood supply observed were dermal trophic changes such as thin, white skin over the shins, sometimes with loss of hair. The toenails were frequently ridged and deformed.

In contrast to these minor effects of ischaemia, major sequelae such as ulceration and gangrene have been uncommon. This was first pointed out by Leriche and confirmed by all subsequent reports; ulceration and gangrene are not a common feature of insidious aortic thrombosis, and should they arise may occur late in the disease. If ulceration does appear it is frequently the result of a small local injury or infection which fails to heal, and the prognosis then immediately becomes more serious. Healing of ulcers and of amputation wounds is difficult, and a distal amputation may be followed by further progressively higher operations. In the present series ulcers of a malleolus were seen in three patients and gangrene of a big toe in two. In one of the latter amputation of a big toe was required and was followed by satisfactory healing. The ages of these five patients were 44, 55, 58, 62, and 63 years—an average of 56.5 years. (Late gangrene also occurred in our oldest patient, aged 78, shortly before death. She died of myocardial infarction and not as a direct result of the aortic thrombosis.) Edwards and LeMay (1955) suggest that obstruction of branches of the aorta may give rise to visceral symptoms, without, however, quoting actual observations. In the present series one patient, a man aged 55, complained of nausea after exercise. He had an aortic occlusion below the level of the third lumbar vertebra. The inferior mesenteric artery was involved, as in most of our cases (see "Radiology" below), but the superior mesenteric artery was patent. The definite association with exercise is unusual and difficult to understand. Visceral symptoms were not encountered in any other cases of our series.

Covey (1955) mentions perineal pain and sacral formications as symptoms in patients with aortic occlusion. No such complaints were made by our patients.

Bonney (1956) and de Wolfe *et al.* (1954) drew attention to cases with atypical claudication of the hip, presenting in the first place as supposed orthopaedic problems.

Symptomless Aortic Occlusion

Finally, a number of cases have been reported in which thrombosis of the abdominal aorta was found at necropsy, having been unsuspected during life. All these patients had been seriously ill and bedridden for some time before death; symptoms of aortic occlusion would therefore not be prominent. It is possible that thrombosis occurred in these cases at a late stage in the illness. Greenfield (1943) reported three such cases; one patient died of miliary tuberculosis, the second of bronchopneumonia, and the third of acute yellow atrophy of the liver. Frelick and Shellenberger (1954) were able to demonstrate aortic occlusion in a patient seriously ill with malignant hypertension; he had had no symptoms referable to aortic occlusion. Evidently symptoms need not normally be expected unless the patient is mobile, when the demand for oxygen by the muscles will exceed the supply. The following history, however, is of interest in this connexion.

Case 4.—The patient had an attack of paralytic poliomyelitis at the age of 21. This left him with paralysis of both legs and he has since been confined to a wheel-chair. When he was 47 he began to complain of pain in the left foot; this later spread to involve both legs. The pain was always worse at night. Examination revealed absence of femoral pulses and an aortogram proved the presence of aortic thrombosis.

The reason for his continuous rest pain is uncertain. It may be that because of his immobility there was lack of stimulus for the development of a collateral circulation, and that long disuse had been followed by hypoplasia of the vascular supply to the legs. When thrombosis supervened, therefore, the blood supply to the wasted muscles or tissues became insufficient even for their resting demands.

The most obvious sign to inspection is the profound wasting of the lower limbs and buttocks. It is not always present, however, and presumably takes some time to develop. It has already been mentioned, together with skin and nail changes, loss of hair, and possibly ulceration.

Undoubtedly the most important sign is loss of palpable arterial pulsation below the block. The femoral arteries are never felt to pulsate, nor, in our experience, the popliteal, dorsalis pedis, or posterior tibial arteries. Pulsation below arterial obstruction is said to occur at times when the patient is at rest; this disappears after exercise. The absence of pulsation in the femoral arteries does not imply that they are necessarily occluded. Arteriograms nearly always show these vessels to be patent even though no pulse is felt in them. The phenomenon is due to filling from numerous small collaterals, carrying blood over unequal distances from the aorta over a tortuous course, and producing damping of the pulse. The position is the same as in coarctation of the aorta, where the femoral pulse is usually impalpable but femoral blood flow is present.

Confusion may at times be caused by strongly pulsating collaterals in the groin. We have not encountered it to any serious extent, though faint pulsations have been felt in the groins of some patients in an unusual position, and clearly not caused by the femoral arteries. Burt *et al.* (1952) state, however, that pulsation in an inferior epigastric artery may at times be strong enough to be mistakenly attributed to the femoral artery. These authors also mention the possibility of an anatomical anomaly in which one external iliac artery arises direct from the aorta at a high level and thus fails to be occluded by thrombus lower down.

In patients with a thin abdominal wall the level of the aortic block can sometimes be made out by palpation. Above the block pulsation of the abdominal aorta may be particularly vigorous. It should be borne in mind, however, that the level of the aortic bifurcation is somewhat variable, and an apparent "block" may be due to a high bifurcation. Nevertheless there is little doubt that the actual level of the obstruction can be thus determined in some cases.

The presence of collaterals has already been mentioned. They may sometimes be seen and felt in the groins and lower abdominal quadrants, but on the whole are not prominent. They are not so widespread as in patients with coarctation of the aorta.

Burt *et al.* (1952) state that in most cases of aortic thrombosis neurological disturbances will be found, consisting not

only of wasting but also of fasciculation and "stocking" analgesia. We have certainly observed these signs in a number of patients.

Covey (1955) described as a sign of aortic thrombosis a loud musical systolic murmur over the spinous processes of the lumbar vertebrae and lower abdomen. He found this sign in two out of four patients. In this connexion it is of interest to note the apparently contradictory claim made by Edwards (1952), according to whom a systolic murmur may frequently be heard over an arteriosclerotic vessel, but disappears when this vessel becomes occluded. It may be inferred that the murmur described by Covey is a result of the collateral circulation. Since reading his article we have had an opportunity to examine ten patients with aortic thrombosis with particular reference to murmurs; a soft blowing systolic murmur over the lumbar region was heard in four. DeBakey *et al.* (1954) also observed similar murmurs over the lower abdomen.

Haematuria resulting from emboli into the kidneys is mentioned as a sign by Straus *et al.* (1946). It does not seem to have been observed by others.

Plethysmography and Ballistocardiography

We have no personal experience of plethysmography in this condition, and are therefore unable to discuss this procedure. It was not carried out in the majority of cases, and it seems unlikely that much of value was lost by omitting that investigation. The same applies to the use of the ballistocardiogram. Elkin and Cooper (1949) described changes in the tracings which they implied were characteristic, but their work does not seem to have been followed up. In view of the more complete information obtained by arteriography, these indirect methods would seem unnecessary refinements.

Associated Cardiovascular Disease

In the present series there were six patients with mitral stenosis and auricular fibrillation. These will be described separately (Starer and Sutton, in preparation). One further patient, a male aged 55, had suffered a coronary thrombosis several years before his admission to St. Mary's Hospital.* In the other patients clinical, radiological, and electrocardiographic examination failed to reveal any evidence of heart disease. Theis (1952) in his report on 29 patients stated that cardiac disease or anaemia was present in 75%, without, however, giving further details. A high incidence of heart disease was also found by Burt *et al.* (1952). Little mention of associated cardiac disease is made in the recent papers from surgical clinics (for instance, DeBakey *et al.*, 1954), presumably because of selection of patients reaching those clinics.

Hypertension is not particularly associated with aortic thrombosis. There are some patients, however, who have hypertension which is related to aortic thrombosis. These form an important group, and space is given to some discussion of this problem below. Of the present series, the diastolic pressure was below 90 mm. Hg in 18; from 90 to 100 mm. in 8; from 100 to 110 mm. in 4; and above 120 mm. in 2 patients.

Thrombophlebitis and pulmonary embolus have been mentioned as frequently associated conditions (Elliot and Peck, 1952). One of our patients, whose case is described in more detail later, developed recurrent attacks of thrombophlebitis at an early stage of his disease. No pulmonary emboli have been encountered in our patients.

Length of History

It is now well recognized that the history in these cases may extend over many years. Beaconsfield and Kunlin (1953), for instance, quote the case of a patient who is believed to have had symptoms due to aortic thrombosis for 21 years. In the present series the longest history was 13 years. The following table shows the length of history in the 32 cases:

Length of History (Years)	No. of Patients	Length of History (Years)	No. of Patients
13	1	4	5
8	3	3	4
7	1	2	2
6	1	1	1
5	1	Less than 1	13

Examination of the histories of many of these patients suggests a relatively rapid evolution of symptoms over a period of months in the early stages. Thereafter symptoms remain unchanged or progress very slowly.

Diabetes Mellitus

No cases of diabetes mellitus were encountered in the present series.

Radiology

Plain Radiographs

The plain radiograph has little importance in the diagnosis of aortic thrombosis. The presence or absence of calcification in the abdominal aorta is of no help. It was thought that the tortuous and dilated lower intercostal and subcostal arteries which develop as part of the collateral circulation might cause notching of the lower ribs. This is seen in some of the rare cases of coarctation of the abdominal aorta. However, examination of the radiographs in our cases has failed to reveal this sign. Aortography shows that the tortuosity of the intercostal and subcostal vessels in these cases is not as marked as in coarctation. (See Special Plate, Fig. 1.)

Aortography

Aortography is the most useful procedure in making a positive diagnosis, and all our patients were so examined.

Price and Wagner (1947) are often credited with being the first to have used aortography to demonstrate thrombosis of the abdominal aorta. They examined two patients during 1945, and in the second patient were able to confirm their radiological diagnosis at necropsy. However, Leriche in his original paper already refers to cases in which aortography has been performed in his clinic before 1942. Since 1947 the method has been used increasingly. The diagnosis from bilateral iliac occlusion cannot be made with certainty without aortography (except, of course, at operation or post mortem), and the earlier case reports suffer to some degree from this diagnostic uncertainty.

In this connexion it may be useful to mention some of the pitfalls of clinical diagnosis. In our experience it is not possible always to distinguish clinically between thrombosis of the lower aorta and bilateral thrombosis of the common iliac arteries. This was also found by Milanés *et al.* (1952). We see this error made from time to time by experienced physicians and surgeons. Further, one may be misled by pulsation in a groin into believing that the femoral pulse is present, when in fact one is feeling a dilated collateral—for example, the inferior epigastric; or the disposition of vessels may be unusual.

The two constant features which between them make a diagnosis at aortography certain are an abruptly ending column of contrast medium, the block lying anywhere between the level of the renal arteries and the aortic bifurcation; and the presence of a collateral circulation. When the block is well below the origin of the renal arteries the aorta below these arteries was generally narrow and tapering. The narrowing thus produced was distinctly in excess of the normal diminution of calibre of the lower aorta. About half of the patients in the present series had aortic occlusions well below, the rest directly below, the level of the renal arteries (Fig. B and Special Plate, Figs. 2–4).

In five patients the aortic thrombus appeared to be extending into one or other renal artery (Fig. B and Special Plate, Fig. 5). This appeared on the aortogram as an area of narrowing or a filling defect at the mouth of the renal artery. In the remaining patients, however, thrombus had stopped just short of these arteries. Extensive renal arterial

*Another patient with a history of previous coronary thrombosis has been encountered amongst eight further cases seen since this paper was written.

involvement is likely to be rapidly fatal, but appears to be uncommon. No such cases have been seen in the Pathology Department at St. Mary's Hospital; consequently we believe that the progress of thrombosis is often slowed or halted on reaching the renal arteries. This suggests that spreading aortic thrombosis is a self-limiting disease in the large majority of patients. The reason for this is not altogether clear. When the iliac arteries become blocked the

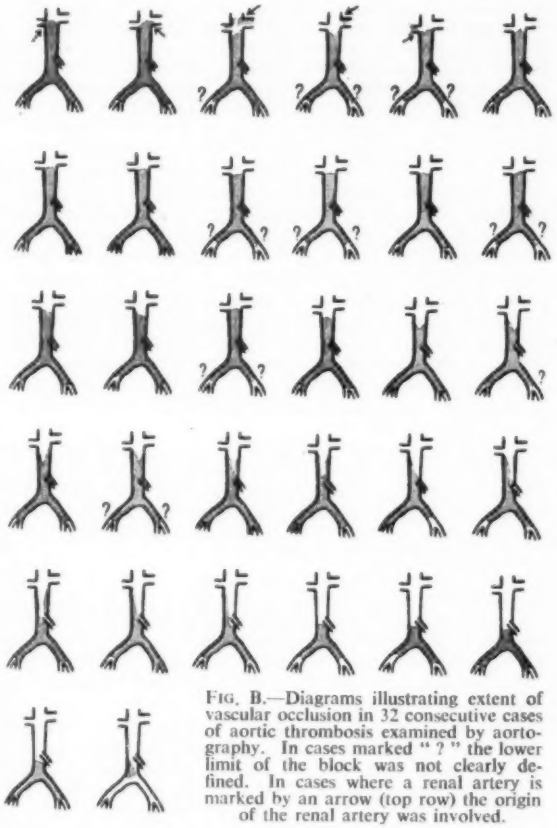

FIG. B.—Diagrams illustrating extent of vascular occlusion in 32 consecutive cases of aortic thrombosis examined by aortography. In cases marked "?" the lower limit of the block was not clearly defined. In cases where a renal artery is marked by an arrow (top row) the origin of the renal artery was involved.

effluents from the aorta below the renal arteries are relatively small, and a cul-de-sac is formed in which clotting can proceed rapidly and easily. At the level of the renal arteries, however, flow is torrential and clotting cannot take place so readily. Whether the degree of atheroma found at different levels in the aorta plays any part is uncertain, but it is true that atheroma maximally involves the lower abdominal aorta below the renal arteries. As thrombosis extends upwards the lumbar arteries and inferior mesenteric artery become occluded. Involvement of the latter vessel is not, as a rule, associated with any symptoms to mark its occurrence. Blood is carried from the superior mesenteric artery through its middle colic branch to the left colic branch of the inferior mesenteric artery and hence to the superior haemorrhoidal artery. These anastomotic vessels form a very constant and characteristic loop in the left upper quadrant (Special Plate, Figs. 1, 4, 5, 6). Theis (1952) has reported one death from gangrene of the bowel as a result of inferior mesenteric arterial thrombosis; this appears to be unique.

The anastomotic channels in aortic occlusion have been extensively described by Burt *et al.* (1952) and by Edwards and LeMay (1955). It is unnecessary to describe them in detail here. Although lumbar aortography gives some idea of the extent of the collateral circulation, it is unable to show the anastomosis in the anterior abdominal wall deriving from the internal mammary arteries. Further, the extent of filling may depend on the phase at which the radiographic exposure was made. We have not found it possible to correlate the degree of the patient's disability with the extent of the collateral circulation as shown by angiography.

In most of our cases the common iliac arteries were occluded, and flow could be seen to start about the iliac bifurcation (Special Plate, Fig. 7). In one patient thrombosis extended to the commencement of the femoral artery (Special Plate, Fig. 6). Rarely the internal iliac artery appeared blocked when the external iliac artery was patent, or vice versa. Frequently a large anastomotic vessel may be seen entering the iliac arteries at the level where flow recommences. This occurs often enough to suggest that the lower limit of the block is determined by collaterals able to carry sufficient blood into the iliac arteries, thereby producing a relatively fast flow of blood which will prevent clotting.

An idea may be gained of the extent of the collateral circulation required when it is remembered that the quantity of liquid flowing through a tube is as the fourth power of the radius (Poiseuille's law) and comparing the radii of the blocked aorta with even the largest collateral.

In addition to the aortic block it may be possible to demonstrate additional and unsuspected blocks in distal leg arteries, a point of great importance in assessing prognosis and treatment.

Case 5.—Male aged 56. This man had suffered from progressive intermittent claudication, beginning in the right and spreading to the left calf, for 18 months. The legs were cold, but there was no ulceration, muscle wasting, or impotence. The femoral pulses could not be felt. A clinical diagnosis of aortic thrombosis was made. It was confirmed by aortography, and incidentally the presence of a horseshoe kidney demonstrated. There was, however, in addition occlusion of the left popliteal artery, well shown on the serial films.

Similar cases have been described by DeBakey *et al.* (1954).

Complications of Aortography

While it is proper to stress the diagnostic importance of aortography, it should be pointed out that it is a procedure which involves discomfort to the patient and carries an appreciable morbidity (McAfee, 1957). It is not an examination to be undertaken casually by the inexperienced, whether radiologist or surgeon.

The interpretation of films is, on the whole, straightforward, but Gaylis and Laws (1956) have pointed out that appearances superficially similar to those due to aortic occlusion may be obtained by subintimal injection of the contrast medium. The absence of anastomotic vessels and the persistence of the contrast medium in rapid serial films should help to avoid this diagnostic error. It should be added, however, that in a large experience of aortography by one of us (D. S.) this accident has proved very rare.

Brock (1953) has expressed the fear that puncturing the aorta may lead to an extension of thrombosis. He quotes the history of a young female patient of his own in support of this. The danger must, however, be very remote. We have seen no evidence of further spread following arteriography, and related to it, in the cases we describe, nor has thrombosis ever developed in any of the many patients without aortic thrombosis on whom aortography has been carried out at this hospital. It must also be kept in mind that thrombus in the occluded aorta may tend to spread even when nothing is done to that vessel, and that spread consists in a building up of the pre-existing clot. This appears to have happened in Brock's patient. Thrombosis in relation to the needle puncture might reasonably be expected to occur at the site of puncture, which is several inches above the level of the block. This in fact does not occur, and we do not consider extension of thrombosis to be a serious hazard of aortography.

Among the complications of aortography described, the most important is undoubtedly anuria and renal failure (Dormandy *et al.*, 1957). At least 12 deaths from this cause are now recorded in the literature.

A recent survey (McAfee, 1957) suggests that there is a greater danger of renal complications in cases of aortic thrombosis than in others. This is because, with the blockage of the aorta, a much higher proportion of the contrast medium enters the kidneys than would normally do so. As a result there is a greater risk of a toxic dose being delivered to the kidneys. We are also aware of at least one unpublished instance at another London hospital where aortography in a case of aortic thrombosis was followed by renal failure and death. In our own large series of cases of aortic thrombosis in which aortography was performed we have not encountered any such complication. However, there is no question that extra caution as regards the dose injected is needed in these cases, and we would stress that adequate diagnostic results can be obtained using only 15–20 ml. of 60% "urografin." With doses such as this we do not think there is any real danger of renal damage.

Paraplegia following aortography has also been recorded several times, and is discussed in detail by Hare (1957). Other complications which have been noted are pneumothorax, perforation of the bowel, peritoneal injection, and haemothorax.

All these recorded complications serve to emphasize that aortography is not a procedure to be lightly undertaken by the occasional dabbler. The incidence of complications in aortography does, in fact, appear to be directly related to the experience of the operators.

At St. Mary's Hospital, where large numbers of aortograms are performed, the procedure is normally carried out by the radiologists in the *x*-ray department under strictly standardized and controlled conditions. Morbidity and complications have been thus reduced to a minimum. In the past four years some 500 aortograms have been undertaken, mainly on patients with arterial disease. The only significant complication encountered has been the single case of temporary anuria mentioned above (Dormandy *et al.*, 1957).

Thus, provided adequate precautions are taken and the problem of dosage is fully understood, aortography in suspected cases of aortic thrombosis is fully justified. This is emphasized by the confidence with which these cases are entrusted to us for investigation by our colleagues.

Discussion

Aetiology

Mitral Stenosis.—Six of the present patients had mitral stenosis and auricular fibrillation. In these there was evidence of multiple emboli. They will be discussed in detail elsewhere, and we shall bring forward evidence for believing that in these cases the aortic thrombosis was a result of more distal emboli causing retrograde clotting into the aorta (Starer and Sutton, in preparation). Four of these six cases were in women—that is, half the female cases in the series.

Trauma.—In three cases described above aortic thrombosis may have been related to trauma, but the relationship is uncertain.

Atheroma.—There would seem to be little doubt that in most of our cases thrombosis was superimposed on underlying atheroma. Previous pathological findings and our own arteriographic experience show that this is the case. A study of our arteriographic material leads us to believe that thrombosis usually starts in the common iliac arteries. This appears to be the general opinion also of other writers on the subject—for instance, Leriche (1951). The reason for this is not known. Straus *et al.* (1946) consider that thrombosis is facilitated by heavy atheroma in that region caused by local eddy currents. Like Leriche, we have, however, seen thrombosis starting at a higher level, and we have even observed occasional patients with localized atheromatous stenosis of the aorta and apparently healthy iliac vessels at aortography. This can give rise to a most puzzling clinical and radiological picture, particularly in a young patient. It may be extremely difficult to differentiate from the very rare syndrome of coarctation of the abdominal aorta. Despite these exceptional cases, it is clear that, as already stated, most cases result from atheroma affecting the common iliacs and terminal aorta.

Case 6.—A 55-year-old gravedigger. He had been complaining of intermittent claudication for ten years, beginning on the right but finally involving both calves and thighs. More recently he had also suffered from pain at rest, but there had been no impotence or muscle wasting. A bilateral lumbar sympathectomy (L 1–5) produced no change. An aortogram in January, 1956, showed partial occlusion of the aorta 1½ in. (3.75 cm.) above the bifurcation and complete occlusion of the right internal iliac artery (Special Plate, Fig. 8). Between January and December, 1956, there appeared to have been no change in his condition. But, since his disablement was severe, disobliteration of the aorta and iliacs was carried out (Mr. Eastcott). At operation complete occlusion of the aorta was found up to the level of the renal arteries. (It may be noted that the level of puncture was considerably above the level of the occlusion.) A successful disobliteration was achieved.

We have not studied blood cholesterol levels in our patients. Theis (1952) reported that 62% of his patients had a cholesterol level above 300 mg. per 100 ml. of blood. Of greater significance may be the studies on serum lipoprotein concentrations carried out by de Wolfe and his colleagues (1954, 1956). In a study of 84 non-diabetic subjects with peripheral aortic atherosclerosis they found in about half the cases an increase in cholesterol and low-density lipoproteins with a decrease in high-density lipoprotein content as compared with normal subjects. The increase was greater in patients with aortic than in those with femoral occlusion.

Not all writers have accepted the atheromatous origin of aortic thrombosis. Leriche's view seems to have been that it was probably the result of a peculiar arteritis. The arguments in favour of this are summed up by Shapiro (1952), who mentions the following points: (1) thrombosis is rare, whereas atheroma is common; (2) thrombosis begins in the iliac arteries, whereas atheroma is maximal in the aorta; (3) age—these patients tend to be middle-aged and have not reached the period of most advanced degenerative change; (4) the presence of a definite arteritis in some cases; and (5) the presence of an intensive periarteritis. Similar views were expressed in the discussion following the paper of DeBakey *et al.* (1954). It should, however, be remembered that marked cellular infiltration and intensive periarteritis are found in relation to atheromatous occlusion of vessels. Several case reports exist of aortic thrombosis due to alleged Buerger's disease. Bohle (1950), for instance, reported two such cases, neither of which showed any other manifestations of thromboangiitis obliterans. His interpretation of the histological appearances must be treated with reserve, since the appearances could equally well be due to the cellular reaction often seen in relation to a thrombosed atheromatous vessel. We have, however, seen one patient with a history compatible with Buerger's disease who developed aortic thrombosis.

Case 7.—A male aged 38, diagnosed as a case of Buerger's disease because of arterial insufficiency to the legs with repeated attacks of phlebitis. The femoral arteries appear to have been normal, and his blood pressure 125/60 mm. Hg. A lumbar sympathectomy was carried out without benefit; following this operation femoral arterial thrombosis was diagnosed. He developed increasingly severe intermittent claudication and impotence and began to complain of headaches. A diagnosis of aortic thrombosis was made, and his blood pressure was found to have risen to 180/110 mm. Aortography demonstrated aortic occlusion at the level of the renal arteries, and the left renal artery was narrowed at its origin. Resection of the thrombosed segment of aorta was carried out and a polyvinyl graft inserted; at the same time a left nephrectomy was performed (Professor Rob). There was marked alleviation of symptoms and the blood pressure fell to normal levels. Pathological examination of the excised aorta suggested atheroma as the underlying abnormality. Here also Buerger's disease could not definitely be implicated. Histologically, the kidney showed changes of chronic pyelonephritis, but no arterial changes as are seen in hypertension.

Other Aetiological Factors.—A large number of other possible aetiological factors have been mentioned. Gross

and Philips (1940) found one case complicating dissecting aneurysm. Pinkerton (1948) reported an 81-year-old man in whom the aorta was pressed on by extensive spinal osteophytes and these may have been responsible for aortic thrombosis; the author recalls the subclavian and brachial thrombosis resulting from pressure by a cervical rib or a crutch. We have observed similar cases associated with large osteophytes, but doubt whether it was a significant aetiological factor. Horwitz (1948) observed thrombosis of the aorta in a 58-year-old woman with Addison's disease occurring shortly after the performance of a Cutler test. Syphilitic aortitis has been recorded on a number of occasions as an aetiological factor (Greenfield, 1943; Beaconsfield and Kunlin, 1953), but was not found in any of our cases. Rothstein (1935) gives a lengthy list of conditions that have been found together with aortic occlusion; their relationship is not always clear. Dexter *et al.* (1957) described a patient with aortic thrombosis who also suffered from Marfan's syndrome. Finally, Harrison *et al.* (1955) report a remarkable and unique family history: aortic thrombosis occurred in two brothers and one cousin, while four other members of the family had severe arterial insufficiency of the legs.

Unusual associated conditions found in our series were fused kidneys in two cases and poliomyelitis in one case. Of the two patients with fused kidneys, one had a horseshoe kidney (Special Plate, Figs. 2 and 7), the other a crossed fused ectopia. The pelves of the fused kidneys in this latter case contained staghorn calculi, and the patient also suffered from cysteinuria and retinitis pigmentosa.

Hypertension

The relationship between aortic occlusion and hypertension is of considerable interest and merits further discussion. Raised blood pressure is a common finding in the general population, and therefore a number of cases of aortic thrombosis may be expected to have incidental hypertension. In so far as a raised blood pressure predisposes to atheroma it may become one aetiological factor in aortic thrombosis. We have already remarked on the relatively small number of patients with aortic thrombosis who also have hypertension.

A second possibility is that occlusion of the aorta below the renal arteries in itself is responsible for a rise in blood pressure. This possibility seems to have attracted several German authors (see Bohle, 1950; Krautwald *et al.*, 1955). Brotcher (quoted by Horwitz, 1948) obtained small rises in blood pressure in dogs by clamping the aorta below the origin of the renal arteries. Apart from this, however, there appears to be little experimental or clinical evidence to support this view of hypertension in aortic occlusion. The absence of hypertension in so many of these patients, on the contrary, is definite evidence against it.

The third possibility, and the one of the greatest interest, is that hypertension of renal origin may be caused by narrowing of a renal artery from extension of thrombus. Goodman (1952) has given an excellent account of the occurrence of the Goldblatt kidney in man. The kidney supplied by the occluded artery remains histologically normal, being protected by the arterial obstruction—a state of affairs similar to that found in experimental hypertension in rats (compare Case 7). Such hypertension, if treated early, should be reversible by nephrectomy.

We have observed renal arterial stenosis on five occasions. In one of these patients the right renal artery and right kidney were abnormally small, but appeared to function normally. This patient died following an attempted grafting operation, and at necropsy the kidney was considered to be congenitally hypoplastic. Of the five patients mentioned above, two had normal blood pressure. Similar cases are reported in the literature, and narrowing of the renal artery is obviously not always associated with hypertension. One patient was mildly hypertensive, and the relationship between raised blood pressure and renal arterial involvement is not clear. One patient has already been described (Case 7); the history of another is of some interest.

Case 8.—A 38-year-old woman of gipsy origin. Four and a half years before admission to St. Mary's Hospital she awoke one night complaining of tingling in both legs. This seems to have been only transient, and she was subsequently well enough to work on a farm. Three years later she suddenly developed pulmonary oedema, and she was found to be hypertensive. Cardiac failure persisted, and a year later her hypertension had become frankly malignant. Her blood pressure was 220/120 mm. Hg, there were retinal haemorrhages with blurring of the optic disks, and proteinuria was present. She was admitted to the local hospital, where a diagnosis of phaeochromocytoma was made and an operation for its removal performed. No such tumour could be found, but it was noticed that the aorta was not pulsating. The diagnosis was changed to one of aortic thrombosis and the patient transferred to St. Mary's Hospital. Here an aortogram showed aortic occlusion at the level of the renal arteries: the right renal artery appeared to be blocked (Special Plate, Fig. 5). Renal catheter studies, however, showed some function of the right kidney. At a later date the abdominal aorta was excised (Professor Rob and Mr. Eastcott) and replaced by a freeze-dried graft. On the day following operation her blood pressure was 280/170 mm. It was lowered to 230/110 mm. by hexamethonium. She was discharged at her own insistence before further blood-pressure or renal-function studies could be carried out, and it has not been possible to follow her up further.

Reports of similar cases are now sufficiently frequent to make it clear that aortic thrombosis may be a factor in the inception of malignant hypertension. The physician dealing with such a case must consider this possibility, and aortography would seem to have a limited place in the investigation of these patients. Martorell (1954) described two deaths from malignant hypertension in patients with aortic thrombosis and renal arterial involvement, and two others cured by operation. Roberts (1955) operated successfully on a similar case. Krautwald *et al.* (1955) studied one such case in which both renal arteries were involved. They found normal inulin clearance, but reduced renal plasma flow. The filtration fraction was increased. On the basis of comparison with "ordinary" hypertensives the authors conclude that renal blood flow in this case was diminished beyond that otherwise seen. Price and Wagner (1947) reported a case of malignant hypertension in which there was bilateral occlusion of polar arteries. Other cases have been reported by Frelick and Shellenberger (1954) and by Barnett *et al.* (1952).

The combination of hypertension and absent femoral pulses found in these cases clearly require differentiation from coarctation of the aorta.

Impotence

The nature of the inability appears to be failure to maintain an erection. This was so described by Leriche in his original publication. It is presumably due to failure of adequate blood supply to the corpora cavernosa through the internal pudendal artery. In those patients who develop an adequate collateral supply to that artery impotence does not develop. Presumably it is the development of such a collateral circulation following sympathectomy or grafting which may bring about the disappearance of this symptom; or the natural improvement in the collateral circulation with time, as appears to have happened in one of our cases. With regard to lumbar sympathectomy, it should be remembered that bilateral section below L 2 abolishes ejaculation, though erection and sensation may remain normal.

An alternative mechanism is discussed by Straus *et al.* (1946). They postulate that weakness of lower limbs, especially after exercise, may be due to Dejerine's syndrome or "intermittent claudication of the cord," and that this may also result in impotence. A lesion involving the sacral nerves below S 1 abolishes erection and produces relative anaesthesia of the penis (impotence may be found in cauda equina tumours, presumably a somewhat comparable situation). Burt *et al.* (1952) have, however, drawn attention to the fact that disturbances of micturition are not found in aortic thrombosis, and would be expected in cord lesions at the level demanded to cause impotence.

Johnson (1954) reported testicular atrophy found at necropsy in one man. We have seen one patient who,

clinically, appeared to have somewhat atrophic testes; histological examination showed them to be normal, however. We have not had an opportunity to estimate the serum gonadotrophin level in any of our cases; this may be not without interest. In fact the testicular artery can frequently be seen on aortograms and the collateral supply to the testes appears good (Neuhof and Mencher, 1940).

Differential Diagnosis

It is our experience that the diagnosis is often—perhaps usually—missed by the doctor referring the case to hospital, and it is part of the purpose of this paper to make the condition better known. If the diagnosis of aortic thrombosis is kept in mind, suspicion should be easily aroused, and a fair degree of certainty in diagnosis readily attained by physical examination. The diagnosis can then be proved unequivocally by aortography.

A number of other conditions may be confused with thrombosis of the aorta. Bilateral iliac arterial thrombosis cannot be differentiated from it without an aortogram. De Wolfe *et al.* (1954) and Bonney (1956) described patients complaining of intermittent claudication of the hip who were referred for orthopaedic treatment with the mistaken diagnosis of hip-joint disease. We have seen one patient diagnosed and treated for some time as a case of sciatica. Progressive muscular wasting may suggest a primarily neurological lesion, and the finding of impotence, peroneal pain, fasciculation, and sensory loss apparently confirm it. The patient whose main complaint is impotence may well be referred to a psychiatrist for lengthy and fruitless treatment. Vigorous aortic pulsation above the block may suggest the presence of an aortic aneurysm—an error of less importance.

When hypertension is present a number of considerations arise. We have described a case in which a mistaken diagnosis of phaeochromocytoma was made. It has also been suggested that in patients with hypertension the absent femoral pulses may lead to an erroneous diagnosis of coarctation. The presence of intermittent claudication and other features noted above should prevent such an error. Also, as previously mentioned, rib-notching, even in the lower ribs, does not seem to occur in aortic thrombosis.

We believe that the diagnosis of aortic thrombosis is sometimes considered and dismissed because of the absence of gangrene. It is therefore worth emphasizing that nutritional changes in the lower limbs are the exception rather than the rule, and that a diagnosis of aortic thrombosis is perfectly compatible with a normal nutritional state of the feet.

Prognosis

The first report of aortic thrombosis appears to have been that by Severinus in 1632, made as a result of post-mortem examination (for a history of aortic thrombosis see Burt *et al.*, 1952). The scanty reports following this were similarly based on post-mortem examinations, and in 1935 Rothstein was able to collect 123 cases from the literature with an alleged 91% mortality. It should be remembered that before the introduction of aortography and the development of major vascular surgery the diagnosis in the living subject had to remain speculative. As a result the impression of aortic thrombosis as an inexorably fatal disease arose. It was perhaps only to be expected that a block of the major vessel should give rise to rapid gangrene and death. In 1942 Leriche published his experience with such cases, and pointed out that the outlook for these patients was by no means hopeless. From his article it is evident that he had the greatest difficulty in persuading his colleagues in France of the correctness of his observations. While, in general, it is now agreed that his description of the clinical picture in aortic thrombosis was substantially correct, the earlier and gloomier view still lurks in the background. That disablement is severe is without doubt; we also know that some of these patients will die from renal involvement or gangrene. Nevertheless, from our review of the condition it is clear that the danger to life has been grossly exaggerated in the past, and that most patients with aortic thrombosis can continue to lead useful and moderately active lives for many years. Indeed, there is some evidence that the patient is more likely to succumb to associated coronary vascular disease or other illness than to the aortic thrombosis.

Recent advances in arterial surgery have made operative treatment of aortic thrombosis a practical procedure, and many such operations have now been performed at St. Mary's Hospital. The assessment of the long-term results in vascular surgery is not yet possible, and is in any case outside our province. It is clear, however, that the dangers of major surgery in these patients, who are often very poor operative risks, must be carefully weighed against the prognosis of the untreated disease. This, as we have pointed out, is less gloomy than has been generally believed.

Summary

A clinical and radiological study is presented of patients with aortic thrombosis examined by aortography at St. Mary's Hospital in the four years prior to June, 1957, and the previous literature on the subject is reviewed. During the period under review 32 patients with this condition were examined. (A further eight cases have been seen since this paper was written, bringing our total to 40 cases in five years.)

The clinical and radiological findings are discussed in detail.

The diagnosis should be readily suspected on clinical grounds, but differentiation from bilateral iliac thrombosis is not possible without aortography. The latter procedure has been carried out in all our cases without complication. It is considered that the recorded hazards of aortography have been mainly due to faulty techniques.

Aortic thrombosis is nearly always due to atheroma of the lower abdominal aorta and the iliac vessels. Buerger's disease and other forms of "aortitis" which have been cited as responsible in previous papers are considered to be of little importance. There was a possible relationship to trauma in three of our cases. In six cases aortic thrombosis was associated with mitral stenosis. In these cases retrograde thrombosis was considered to have followed peripheral emboli.

The problem of renal arterial involvement is discussed in detail, together with its possible relationship to hypertension.

It is concluded that aortic thrombosis is neither as rare nor, in most cases, as dangerous to life as was previously thought.

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PATHOLOGICAL STUDY OF THE LIVER IN KWASHIORKOR*

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[WITH SPECIAL PLATE]

In Calcutta a syndrome is frequently seen in children which presents a picture of severe malnutrition characterized by diarrhoea, wasting, oedema of varying degree without gross albuminuria, glossitis, anaemia, cutaneous changes with black pigmentation, enlargement of the liver, hypoproteinaemia, eye lesions of vitamin-A deficiency, failure of growth, sometimes mental changes, and anomalies of hair growth (Fig. A). A similar syndrome has also been observed in parts of tropical Africa, and was described under the name "kwashiorkor" by Williams (1933, 1935, 1940). It has also been called infantile pellagra (Trowell, 1937, 1940, 1941), malignant malnutrition (Trowell, 1944; Trowell and Muwazi, 1945a), ariboflavinosis (Hughes, 1946), and fatty liver disease of infants (Waterlow, 1948).

In pathological studies of this syndrome in children in Africa, Williams (1935) and Gillman and Gillman (1944) found only fatty changes of varying degree in the liver parenchyma and no necrosis or haemorrhage. Waterlow (1948) considered fatty change in the liver to be a constant accompaniment of the disease; he also observed increase of fibrous tissue from the portal tracts with a tendency to progress to Laennec's cirrhosis.

In serial biopsies in 120 cases of pellagra, all but two in patients over 10 years of age, Gillman and Gillman (1945) found fatty changes in the liver and cirrhosis. In the adults the cirrhosis was preceded by a deposit of haemosiderin in the portal tracts in fatty livers, giving a picture of haemosiderosis or cytosiderosis. Liver puncture showed that fatty liver is as constant a feature of the syndrome as the rash or oedema, and that it develops early before other known complications such as pneumonia, tuberculosis, or gastro-enteritis. Of the 120 cases investigated, 15 (12.5%) had frankly pigmentary cirrhosis, while in 20% the liver was pre-cirrhotic and about 30% showed signs of serious hepatic damage amounting to cirrhosis. In 1% of cases the liver had no recognizable damage. In none of the livers was there necrosis or haemorrhage. In two cases in children not included in the above series there was irrefutable evidence of non-pigmentary cirrhosis.

FIG. A.—Typical case of kwashiorkor in Hindu child aged 2 years 2 months. Oedema and skin pigmentation are well shown.

Achar (1950), who studied 78 cases of severe malnutrition in Madras, on histological examination of 12 cases found an extreme degree of fatty infiltration; in two of these cases there was commencing periportal fibrosis, and in one case diffuse fibrosis around the lobules.

The present paper reports the histopathological findings in the liver in 34 cases of kwashiorkor studied post mortem with a view to elucidating the evolution of cirrhosis from hepatic damage.

Method of Investigation

The gross specimens of liver in all cases were fixed in formalin and kept in No. III Kaiserling solution (glycerin and water). After necropsy small pieces of liver tissue 3–5 mm. thick were immersed in Zenker's fluid for 24 hours, washed in running water for 24 hours, and finally preserved in 80% alcohol in tissue jars. Blocks were made by paraffin embedding from different areas of liver in both lobes and studied. Staining methods were as follows: (1) for routine staining—paraffin sections stained by Weigert's iron-haematoxylin and eosin; (2) for connective tissue—Mallory's aniline blue method; (3) for fat—frozen sections stained with Sudan III and counterstained with haematoxylin; (4) for reticulin—Foot and Menard's method as modified by

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Robb-Smith (1937); (5) for the presence of iron pigment—Gillman and Gillman's (1945) modification of Pearl's method.

Cases were classified, according to the histological findings in the liver, into three groups. Group I includes those in which there was an accumulation of fat and/or dilatation of sinusoids but no evidence of cirrhosis. Only one case showed massive necrosis without any fatty change. Group II includes cases with pre-cirrhotic changes, and Group III those in which the liver showed definite cirrhosis.

Group I: Non-cirrhotic

Livers in this group were whitish in colour and the cut surface was greasy to the touch. They can be further divided into four histopathological subgroups.

Subgroup A

There were nine cases in this subgroup. The histological picture was one of fatty change in the liver; in seven cases a moderate amount of fat was present, occupying half or more of the cytoplasm, and in two cases the whole lobule was affected with marked fatty change. In the latter two cases fat was present in the form of a single large, pale-staining globule filling the entire cell; the nucleus was pushed to one pole and the cytoplasm reduced to a narrow rim compressed against the cell membrane, almost every cell being involved. In fact the livers were so fatty that small pieces of tissue floated in the fixative. There was no necrosis or haemorrhage. Sinusoids were much narrowed (Special Plate, Fig. 1). Portal tracts and hepatic venous terminals were scarcely visible. The reticulum of hepatic cords was not thickened. The fat globules stained an intense red with Sudan III in frozen sections. In tissue stained for haemosiderin very little of the pigment was present in hepatic cells or portal tracts. Of the nine cases in this subgroup, focal round-cell infiltration and biliary proliferation were noted in five.

Subgroup B

In the livers in this subgroup (7 cases) the sinusoids were markedly dilated and contained many red cells. Malarial pigment was found in the Kupffer cells in two cases. Focal necrosis of hepatic cells with round-cell infiltration was present in three cases.

Subgroup C

Livers in this subgroup showed a combination of varying degrees of fatty change with dilatation of sinusoids (Special Plate, Fig. 2). The sinusoids contained red cells. Of the four cases in this category two had coexistent tuberculous infection; in another case there were small areas of focal necrosis in the parenchyma with infiltration of round cells.

Subgroup D

In this subgroup there was only one case, in a Hindu boy aged 2 years whose illness had lasted seven months. The liver weighed 350 g.; it was yellowish-white in colour and of normal consistency. Microscopically, it showed massive necrosis of the hepatic cells so extreme that normal hepatic cords could be found only after prolonged search. The destruction had involved large areas so that there was no zonal distribution of the necrosis. In the affected areas the cells had lost their nuclei; the sinusoids were dilated and contained red cells, many polymorphonuclear leucocytes, and histiocytes (Special Plate, Fig. 3). The biliary tree showed extreme proliferation. The ducts were enormously dilated, producing cystic spaces lined by cuboidal cells with hyperchromatic nuclei. The cells had proliferated and been thrown into folds. The proliferated bile capillaries lay in an oedematous acellular connective tissue. Cells did not show any fatty change. Reticulin stain revealed destruction of reticulum of the hepatic lobules, and with specific connective-tissue stain an increase in collagen fibres in between proliferated bile capillaries was noted.

Group II: Pre-cirrhotic

In this group are included the eight cases in which there were pre-cirrhotic changes in the liver. The lobules showed moderate to marked fatty changes combined with a varying degree of dilatation of sinusoids, which were filled with red cells. Fibroblastic connective tissue was seen arising from the portal tracts and spreading into the liver parenchyma without connecting up the portal tracts, resembling an early stage of cirrhosis. The connective tissue was infiltrated with lymphocytes and there was proliferation of the biliary tree. Staining of the tissue for haemosiderin showed none present in the hepatic cells or portal tracts.

In three of the cases the liver tissues showed focal areas of necrosis without specific zonal distribution; bile-duct proliferation was also present. Evidence of coexistent tuberculous infection was found in two cases.

Group III: Cirrhotic

This group comprises cases in which the liver showed a definitely established cirrhotic condition. These are further subdivided according to whether the cirrhosis was (A) post-infiltrative or (B) post-necrotic.

Subgroup A

There were four cases showing definite cirrhosis of post-infiltrative type.

Case 1.—A Hindu boy of 4 who had had the disease six months. The liver weighed 490 g.; it was pale yellow in colour, with a slightly granular surface and firm consistency (Fig. B). Microscopically, thin bands of cellular fibrous tissue extending from the portal tracts had encircled masses of liver cells, isolating them into lobules, the encirclement being complete in some places and incomplete in others. The hepatic cells showed extreme fatty changes, and the sinusoids in the central and mid-zonal areas of the lobule were greatly dilated and filled with red cells (Special Plate, Fig. 4). In some of the hepatic cells a brownish bile pigment was present. In the portal tracts the fibrous tissue was increased and infiltrated with lymphocytes. The hepatic artery and portal veins were normal. The bile ducts were healthy, their lumen being patent and the lining epithelial cells intact and normal. There was some proliferation of the biliary canaliculi in the region adjacent to the portal tracts. The central veins were normal, and no endophlebitis or thickening was found. Staining of reticulum of the sinusoids showed the sinusoidal capillary bed of the lobules to be normal. Specific connective-tissue stain showed adult connective tissue with monolobular distribution arising from the portal tracts (Special Plate, Fig. 4).

FIG. B.—Liver from Case 1.

Case 2.—A Hindu aged 4 years with a history lasting 1½ years. The liver weighed 200 g.; it was pale yellow in colour, and had a smooth surface and slightly firm consistency. Microscopically, cellular connective tissue extending from the portal tract had encircled masses of liver cells around each lobule, resulting in monolobular cirrhosis. The hepatic cells showed varying degrees of fatty change, and the sinusoids were dilated and filled with red cells. There was no necrosis of the hepatic cells. The central veins were

thickened in places, but without endophlebitis or thrombosis, while in some places they were dilated. No evidence of regeneration of parenchyma was seen.

Case 3.—A Hindu girl aged 1 year with a history of six months' duration. Microscopically, the portal tract showed increased fibrous tissue from Glisson's capsule. There was moderate lymphocytic infiltration, also biliary proliferation around the portal tracts and the fibrous tissue spreading from them. The hepatic artery, portal veins, and bile ducts were normal. The hepatic venous tree was also normal. Silver impregnation of the sinusoidal capillary bed showed a normal reticular pattern in a sinusoidal capillary arising from collagenous tissue of the portal tracts. Staining for haemosiderin was negative in the portal tracts and hepatic cells.

Case 4.—A Hindu male infant aged 5 months. The liver weighed 12 g.; its colour yellowish white, surface smooth, consistency slightly firm. Microscopically, a vascular connective tissue from the portal tracts surrounded the liver lobule, resulting in monolobular cirrhosis (Special Plate, Fig. 5). The hepatic cells showed varying degrees of fatty change in the periphery of the lobule. There was no necrosis. In the central and mid-zonal areas of the lobule the sinusoids were dilated and filled with intact red cells. There was no evidence of regeneration of the hepatic parenchyma. The fibrous tissue from the portal tracts showed moderate lymphocytic infiltration and biliary proliferation.

Comment.—The four cases in this subgroup show monolobular cirrhosis in an extremely fatty liver. No evidence of regeneration of parenchyma was seen.

Subgroup B

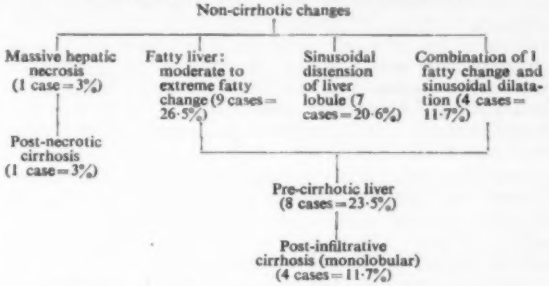
Only one case belonged to this subgroup—that of a Hindu male infant aged 5 months. The liver weighed 150 g., and was yellowish-green in colour, firm in consistency, and with a finely granular surface. Microscopically, fibrous tissue spreading from the portal tracts had surrounded single lobules, resulting in monolobular cirrhosis, while in places there was only increase of fibrous tissue from the portal tracts. The hepatic cells showed complete necrosis with granular acidophilic cytoplasm, nuclei in most areas having completely disappeared (Special Plate, Fig. 6). The necrotic cells contained bile pigment scattered throughout the cytoplasm. Fibrosis had spread from the portal tracts and was slightly infiltrated with lymphocytes; in places the connective tissue was acellular. The portal tracts were difficult to distinguish. Silver impregnation of reticular fibres of the hepatic parenchyma showed thickening of these fibres in the hepatic lobules spreading from collagenous tissue of the portal tracts. Mallory's aniline blue stain showed mature collagenous tissue spreading from the portal tracts, resulting in monolobular cirrhosis; in places fibrous tissue had entered the hepatic lobules. Staining for the presence of haemosiderin failed to demonstrate its presence in portal tracts or hepatic lobules.

Comment.—The picture is one of subacute massive hepatitis leading to post-necrotic cirrhosis.

Discussion

The histopathology has been studied in 34 cases of kwashiorkor in an attempt to follow the development of cirrhosis in this condition. Of the 34 cases, nine (26.5%) showed only fatty change (moderate to extreme in degree), seven (20.6%) sinusoidal dilatation of the liver lobule, and four (11.7%) a combination of fatty change and sinusoidal dilatation. A further eight cases (23.5%) showed a pre-cirrhotic condition of the liver with dilatation of sinusoids and moderate fatty change, and four (11.7%) a definite cirrhotic condition, monolobular in type. No haemosiderin could be detected by special staining of iron in liver tissue. On the other hand, one case showed massive hepatic necrosis and one case post-necrotic cirrhosis. The results of the study can be summarized as follows:

Histopathology of 34 Cases of Kwashiorkor


Non-cirrhotic changes
Massive hepatic necrosis (1 case = 3%)
Fatty liver: moderate to extreme fatty change (9 cases = 26·5%)
Sinusoidal distension of liver lobule (7 cases = 20·6%)
Combination of fatty change and sinusoidal dilatation (4 cases = 11·7%)
Post-necrotic cirrhosis (1 case = 3%)
Pre-cirrhotic liver (8 cases = 23·5%)
Post-infiltrative cirrhosis (monolobular) (4 cases = 11·7%)

Pathological studies of kwashiorkor (Williams, 1933; Gillman and Gillman, 1944) have indicated that fatty change is a constant accompaniment of the disease. Gillman and Gillman (1945), from serial biopsies in 120 cases of pellagra, a syndrome resembling kwashiorkor, observed fatty change progressing to frank pigmentary cirrhosis in 12.5% of cases. In two children not included in the 120 cases the liver showed irrefutable evidence of non-pigmentary cirrhosis.

In the present investigation the fatty liver of kwashiorkor was found to have progressed to Laennec's cirrhosis in 11.7% of the 34 cases, the cirrhosis being of non-pigmentary type. Although four cases in the series showed definite post-infiltrative cirrhosis and one case a post-necrotic cirrhosis, ascites was clinically evident in only two cases. Again, jaundice was not found clinically in any of these five cases. Nine of the 22 cases in Group I (non-cirrhotic) belonged to Subgroup A. In all nine cases cells of the hepatic lobule showed moderate to extreme fatty change with much-narrowed sinusoids. This observation is in conformity with the findings of Gillman and Gillman (1945) in pellagrins in Africa, both infants and adults. Eight cases in the present series showed pre-cirrhotic changes. There were four cases with post-infiltrative cirrhosis, all of them showing fatty change at the periphery of the lobule, while the sinusoids in the central and mid-zonal regions were dilated.

In man fatty liver as a precursor of Laennec's cirrhosis was first observed by Connor (1938) in diabetics. This observation stimulated the study of experimental Laennec's cirrhosis, which showed that prolonged fatty infiltration due to a deficient or unbalanced diet leads to cirrhosis (Rich and Hamilton, 1940; Himsworth and Glynn, 1944a; Chaikoff *et al.*, 1940, 1943). In the present series of 34 cases of kwashiorkor four cases showed post-infiltrative fatty monolobular cirrhosis. Although it may be true that prolonged fatty infiltration leads to cirrhosis, there may be other factors in addition to the fatty infiltration which help the progression to cirrhosis, as has been suggested by Walters and Waterlow (1954), but what these are we do not know.

One case in the present series showed massive hepatic necrosis (Special Plate, Fig. 3) and another had post-necrotic cirrhosis (Special Plate, Fig. 6). Pathological study of the liver by Williams (1933) in kwashiorkor and by Gillman and Gillman (1945) in pellagra showed the absence of necrosis or haemorrhage. Glynn, Himsworth, and Neuberger (1945) have demonstrated experimentally in rats that deficiency of cystine leads to massive hepatic necrosis, the survivors developing post-necrotic scarring and nodular hypoplasia. The inference is that dietetic deficiency of casein causes deficiency of cystine, leading to massive necrosis and post-necrotic scarring. From this it would seem reasonable to suggest that in man severe malnutrition may lead to deficiency of cystine and its effect—massive hepatic necrosis with its sequel post-necrotic scarring.

Again, of the group with non-cirrhotic livers, seven cases showed only dilatation of sinusoids and four showed a combination of dilatation of sinusoids with fatty change. In the eight cases with pre-cirrhotic livers and the four in which there was cirrhosis slight dilatation of sinusoids was also observed. In studies of the pathology of kwashiorkor by Williams (1935) and of infantile pellagra by Gillman and

Gillman (1945) dilatation of sinusoids was never observed; on the other hand, in all fatty livers sinusoids were closed. Gillman, Gillman, Mandelstam, and Gilbert (1945), in rats fed on a diet of mealie pap, the staple food of African children, observed dilatation of sinusoids as a separate pathological finding occurring independently of fatty change and cirrhosis. The finding of dilatation of sinusoids in the present series is a new observation in connexion with studies in human beings.

Out of the 34 cases, in two cases histological examination showed the presence of malarial haemozoin pigment in Kupffer cells, and in four cases there was evidence of tuberculous infection. These are coexistent lesions and play no part in the pathogenesis of the disease.

There are grounds for suggesting that in kwashiorkor there may be deficiency not only of choline but also of both methionine and cystine, resulting in massive necrosis and post-necrotic cirrhosis, though the latter is of rare occurrence (3% in the present series). Although histologically there is fibrosis of the liver in this syndrome, producing a typical picture of cirrhosis, this usually does not present as fully developed cirrhosis with hepatocellular dysfunction and portal obstruction such as is seen in infantile cirrhosis of Indian children, in which the histological picture is different, and has been described by Rao (1935) as subacute toxic cirrhosis.

Summary

Study of the histology of the liver in children suffering from kwashiorkor shows the evolution of cirrhosis from fatty change (post-infiltrative cirrhosis). This is a separate entity of cirrhosis, clinically and pathologically, distinct from the commonly occurring infantile biliary cirrhosis as described by Gibbons (1883, 1890).

Other than fatty change in the liver in kwashiorkor, dilatation of sinusoids may be the only pathological change. Very rarely there may be massive hepatic necrosis and post-necrotic fibrosis.

The clinical part of this work was carried out in the Medical College Hospitals, and the work on morbid anatomy and histology in the Department of Pathology, Medical College of Calcutta. I am indebted to the Principal and Superintendent, Medical College Hospitals, for constant help and kind encouragement.

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THE RENAL LESION IN ANGIOKERATOMA CORPORIS DIFFUSUM

BY

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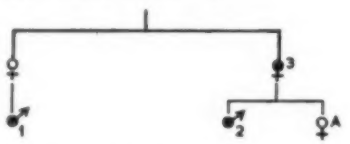
[WITH SPECIAL PLATE]

Angiokeratoma corporis diffusum is a rare disorder first described by Fabry in 1898. About 30 cases have been reported. The literature has been well reviewed by Fessas *et al.* (1955). The disease appears to have a familial incidence and has been reported only in males. It is characterized by multiple small angiokeratotic lesions in the skin, which usually first appear during late childhood. It is also associated with diminished sweating, pains in hands and feet, ankle oedema, proteinuria, renal failure, and hypertension.

Frozen sections demonstrate that there is generalized deposition of a doubly refractile substance; it is found particularly in the smooth muscle cells of the arteries and the heart. It has also been found in the ganglion cells of the brain, lymph nodes, spleen, bone marrow, and kidneys; cells containing a doubly refractile substance have also been found in the urinary deposit. In fixed tissues the cells containing this substance appear distended and vacuolated.

Two further cases of the disease in males in one family are described with particular reference to the renal biopsy findings. A third, female, member of the same family in whom identical renal lesions were found at necropsy is also reported. The three patients (shown in black) are related as follows:



A description of the histological lesions in all three cases follows the case histories.

Case 1

This patient, aged 38, was first seen in September, 1956, complaining of headaches. He had had six attacks of migraine during the preceding year and an occipital headache for two weeks. For three years he had had a noticeable thirst, with nocturia for about three months. Slight ankle oedema had been present for one year. The skin abnormality had been present for as long as he could remember.

Examination

He was a healthy-looking man of normal intelligence. The skin was dry, and on the buttocks, scrotum, penis, medial aspects of thighs, knees, and elbows there were small elevated purple lesions, the smallest about 1 mm. in

diameter. A few small lesions were present on the lips at the muco-cutaneous junction, but none inside the mouth. Incomplete blanching of some of the lesions could be achieved by gentle massage; subsequently they refilled slowly. There was an area of chronic lichenified dermatitis on the outer surface of the left thigh. The ability to sweat was tested by immersing the legs in water at 44°–45° C. The mouth temperature rose from 36.9° to 38° C. Although the patient felt hot, only a little sweating could be demonstrated, and this was only on the nose, cheeks, and forehead. Intradermal injection of carbachol produced only a little sweating in the injected area (anterior chest wall and medial aspect of forearms).

The blood pressure was 210/120 mm. Hg and a chest radiograph showed the heart to be larger than normal; the jugular venous pressure was normal. There was slight bilateral ankle oedema. An electrocardiogram (E.C.G.) showed appearances compatible with left ventricular hypertrophy.

Visual acuity with glasses was 6/9 in both eyes. Slight superficial dystrophic changes were present in both corneae, and there was moderate bilateral hypertensive retinopathy with one small exudate.

Renal Function and Intravenous Pyelogram

Moderate proteinuria and a trace of glycosuria were present at all times; the daily average protein output was 4.5 g. The urine deposit was normal, and chromatography showed only small quantities of normal amino-acids. Blood urea was 48 mg. per 100 ml., and a 24-hour creatinine clearance 48 ml. per minute. The specific gravity of the urine following 24 hours' fluid deprivation and after the intramuscular injection of 5 units of "pitressin tannate" in oil was never greater than 1008. The daily excretion of titratable acid was 27 mEq, and of ammonia 10 mEq. After five days' oral administration of 140 mEq per day of ammonium chloride the *p*H of the urine on the fifth day was 5.14; the total acid excretion on this day was 40 mEq and the ammonia excretion 16 mEq.

An intravenous pyelogram demonstrated kidneys of normal size, shape, and position, with bilateral excretion but poor concentration of dye.

Other Investigations

Serum protein concentration and electrophoretic pattern were normal. Lipoprotein electrophoresis showed an increased β-lipoprotein. The erythrocyte sedimentation rate (E.S.R.) was 20 mm. in the first hour (Westergren). Plasma electrolyte and haematological concentrations were normal. Serum cholesterol 168 mg. per 100 ml. A radiograph of the skeleton showed no abnormalities.

Case 2

This patient, aged 35, was admitted to hospital for investigation after he had been brought to our notice by Case 1. He suffered from bilateral chronic ulcers above both ankles, associated with oedema of the lower legs and ankles, which had been present for over 20 years. The ulcers had never healed for very long, despite much effort, including skin grafts. He thought the widespread skin lesions had always been present, and he stated that he never perspired. For six months he had noticed that he was abnormally thirsty, but he did not complain of polyuria.

Examination

He was a healthy-looking, stockily built man of normal intelligence. The condition of the skin and the distribution of the lesions were the same as in Case 1, except that the characteristic lesions were not present on the legs and that the larger lesions on the genitalia were slightly raised and hyperkeratotic. On the medial side of both ankles there were large, clean, granulating ulcers with sloping edges and considerable induration of the base. These were surrounded by eczematous dermatitis and slight pigmentation. There was also pitting oedema of feet and legs up to the knees. There were no varicose veins, and all pulses were palpable.

The ability to sweat was tested by immersing the arms in water at 42° C., but there was only very scanty sweating on the forehead (about 24 active glands) and no sweating on the arms after removal from the water. Intradermal injection of carbachol (0.07 ml. of 2.5×10^{-4}) on the forearm on two occasions produced only 57 and 50 active sweat glands in 30 minutes (Wada, 1950).

The blood pressure was 125/70 mm. Hg, and a chest radiograph and E.C.G. were normal.

Visual acuity without glasses was 6/6 in both eyes. In both corneae there were curious superficial wedge-shaped opacities of minimal density. The retinal arteries, particularly the smaller ones, were tortuous; the veins showed a definite and striking beading.

There was bilateral firm enlargement of the lymph nodes in the groins. The palate was abnormally high. There was a moderate kyphoscoliosis, but no abnormality of the respiratory system.

Renal Function and Intravenous Pyelogram

Proteinuria was persistent, but was not greater than 1–2 g. in the 24 hours. The urine deposit was normal. The blood urea was 28 mg. per 100 ml., and a 24-hour creatinine clearance was 94.5 ml. per minute.

The concentration of the urine following 24 hours' fluid deprivation was 391 milliosmoles per litre (that is, S.G. 1011 approximately); after the intramuscular injection of 5 units of pitressin tannate in oil it was 375 milliosmoles per litre.

An intravenous pyelogram demonstrated kidneys of normal size, shape, and position, with an excellent concentration of dye.

Other Investigations

The total serum proteins were 7.3 g. per 100 ml.; electrophoresis showed a double globulin band, the slower component being strikingly dense. Lipoprotein electrophoresis had a normal pattern; the lipoprotein was travelling with the faster of the two globulin bands. Electrolyte concentrations in the blood were normal. Serum cholesterol 100 mg. per 100 ml. Haematological examination showed no abnormality, except for a haemoglobin of 12.58 g. per 100 ml. E.S.R. 65 mm. in one hour (Westergren).

Case 3

This woman, who was the mother of Case 2, had died of a cerebrovascular abnormality in 1949 at the age of 47. In view of this her notes and post-mortem findings were obtained to see if she suffered from a similar condition to her son and nephew.

She was admitted to hospital in June, 1949, suffering from apathy and loss of memory for six months. No focal neurological signs were present, and the cerebrospinal-fluid content and pressure were normal. There is no report of any abnormality of the skin. The apex beat was in the anterior axillary line, and a chest radiograph showed an enlarged heart. The urine contained protein, red cells, and granular casts. Three weeks later she became comatose, and it was found that the cerebrospinal-fluid pressure in the lateral ventricles was raised. Various investigations then demonstrated that there was probably an obstruction to the foramen of Munro. The patient died a few days later. Two days before death the blood urea was 80 mg. per 100 ml.

The patient's daughter (A in the diagram) is quite certain that her mother had no rash comparable to her brother's (Case 2); she remembers that her mother's skin was particularly smooth and unmarked.

Necropsy Findings (Professor Crawford)

The body was that of a rather stout middle-aged female. The meninges were normal and there was no evidence of raised intracranial pressure. The blood vessels at the base

of the brain were enormously dilated, the vertebral, basilar, and left carotid arteries being principally affected; the basilar artery was 12.5 mm. wide. The heart was greatly enlarged (weight 630 g.) from hypertrophy of both ventricles. The kidneys (combined weight 240 g.) were reduced in size, and the capsule was stripped with difficulty. The external surface had several large depressed scars, and the cut surfaces showed some irregularity of the cortex.

Renal Histology

Renal biopsies were obtained from Cases 1 and 2 and a post-mortem section of kidney from Case 3. The limited biopsy material and the retrospective diagnosis in Case 3 made it impossible to perform special fat staining on any of these sections.

Case 2 showed what appears to be the essential renal lesions of angiokeratoma: the glomeruli all displayed a fine vacuolation of the epithelial cells of the tuft giving a honeycomb appearance (Special Plate, Fig. 1). Many cells in the loops of Henle and distal tubules showed a similar change (Special Plate, Fig. 2); it was also seen occasionally in Bowman's capsule. In the proximal tubules, by contrast, no significant abnormality was present. A piece of interlobular artery included in the section showed marked intimal thickening with oedema and degeneration of the medial muscular coat, which also contained foam cells.

In Case 3 there were exactly similar lesions in the glomeruli (Special Plate, Fig. 3) and distal tubules; in addition a wedge-shaped area of cortical fibrosis, with glomerular fibrosis, chronic inflammatory-cell infiltration, and marked narrowing of interlobular arteries due to changes in the intima and media similar to those seen in Case 2, was noted.

By contrast, Case 1 showed widespread disorganization of the normal architecture with an increase in interstitial tissue and patchy chronic inflammatory-cell infiltration. Only five glomeruli were present in the biopsy specimen, and three of these were converted into structureless masses. In the two remaining glomeruli there were a few foamy epithelial cells identical with those seen in the other two cases. In this case the proximal tubules showed widespread degeneration with flattening of the epithelium and dilatation of the lumina. The surviving distal tubules also showed atrophic dilatation and nuclear degeneration; some of the cells in the loops of Henle and distal tubules had the foamy appearance already described.

Discussion

The kidneys of all three patients presented identical abnormal histological features. There was distension and vacuolation of the cells of the glomerular tufts and of the distal tubules. Very occasionally a similar change is seen in glomeruli of patients with a severe nephrotic syndrome (Allen, 1951), but it is usually limited to a few isolated cells. Involvement of glomerular cells in lipoid storage diseases is also observed occasionally in Niemann–Pick's disease and in certain types of xanthomatosis. Extensive vacuolation of the glomerular cells combined with a similar change in the cells of the distal tubules, however, does not seem to have been described in any other condition but angiokeratoma. Scriba (1950) and Ruiter (1957) each describe one case of angiokeratoma in which these characteristic renal changes were found at necropsy; in both cases examination with polarized light showed that in the glomeruli and the affected tubules there was a doubly refractile substance which was stainable with scarlet red and Sudan black. It is presumed that this substance is the same as that found in the arterial walls.

The third patient was the mother of Case 2 and the aunt of Case 1, and, though her daughter insists that her mother had a clear, smooth skin, she had the characteristic renal lesions of angiokeratoma. It is probable that Case 3 suffered from the metabolic disturbance with which angiokeratoma is associated, and that therefore this disturbance can occur in women; it also follows that the metabolic disturbance may be present without a skin lesion.

Chronic renal failure occurs frequently in angiokeratoma. Cases 2 and 3 provide the opportunity for studying the lesions before there has been extensive loss of nephrons. The characteristic finding is vacuolation and distension of the glomerular epithelial cells and the loops of Henle and distal tubules. It is evident from Case 3 that these lesions may be present for many years without causing any gross destruction of nephrons. The wedge-shaped area of fibrosis present in this case was associated with typical changes of angiokeratoma in the interlobular arteries. This suggests that the more advanced changes seen in Case 1 are probably the result of these arterial lesions with subsequent glomerular fibrosis and tubular degeneration. The appearances in Case 1, however, are not unlike those of chronic pyelonephritis, and it is possible that the degenerative and ischaemic changes may predispose to renal infection.

Unfortunately, the only information available about the renal function of Case 3 is that just before death the blood urea was 80 mg. per 100 ml. It can only be inferred that a few weeks before, when the patient was conscious, it was probably lower, and that at no time did she suffer from advanced renal failure—an inference compatible with the structural findings. Consideration of the other two cases shows a remarkably close relationship between the renal structural changes and the few renal functional tests that it was possible to perform. Case 2, in which only distension and vacuolation of glomerular and distal tubular cells were present, had a moderate proteinuria, a normal glomerular filtration rate, and gross limitation in the ability to concentrate the urine, due most probably to the deposits in the distal tubules; the blood pressure was normal. Case 1, in which, in addition to the characteristic histological changes, there was considerable destruction of nephrons, had a moderate proteinuria, a low glomerular filtration rate, an even greater impairment of the ability to concentrate the urine, a severe reduction in the ability to increase the excretion of ammonia (another distal tubular function), and hypertension.

Summary

Renal needle biopsy was performed on two men suffering from angiokeratoma. The distinguishing feature was a vacuolation and distension of the cells of the glomerular tufts and distal tubules. In both cases the ability to concentrate the urine was grossly impaired; in one case the glomerular filtration rate was normal and in the other it was moderately impaired.

A retrospective re-examination of the kidney of a female relative of these two patients, who had died some years before, showed identical lesions. Her relatives state that she did not suffer from the characteristic skin lesions. It is possible, therefore, that the metabolic disturbance associated with angiokeratoma can also occur in women, perhaps without the typical skin manifestations.

We wish to thank Mr. W. McKissock and Professor Crawford for permission to publish the findings in Case 3; Dr. A. C. Dornhorst for access to Case 1; Dr. Herxheimer for investigating the disturbance of sweating; and Mr. A. E. Clark for the photomicrographs.

ADDENDUM

Since this paper was submitted the patient in Case 1 has died of malignant hypertension. The post-mortem findings are to be reported elsewhere (Dr. R. G. Shorter). Sections of the kidneys have been stained with Sudan black, and show the presence of lipid in the vacuolated glomerular and tubular cells.

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VITAMIN-D-RESISTANT OSTEOMALACIA

BY

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[WITH SPECIAL PLATE]

Rickets in childhood and osteomalacia in adults are generalized disorders of bone in which the primary osseous defect is a lack of ability to calcify osteoid bone matrix. The essential biochemical abnormalities consist of a reduced serum inorganic phosphorus level, a low or normal serum calcium level, and a raised serum alkaline phosphatase. Radiologically there is usually generalized demineralization, with the well-known rachitic changes at the growing bone-ends in childhood, and with spinal compression and multiple lines of rarefaction, or pseudo-fractures (Looser's zones), in the adult.

Osteomalacia (using the term now to include rickets) may be produced by a lack of absorption of calcium and phosphorus from the gut. In this intestinal group there may be a simple lack of vitamin D, or an inability to absorb the vitamin and the minerals because of an intestinal disorder associated with steatorrhoea. In the renal tubular group there is a normal intestinal absorption of minerals, but an increased loss of either calcium or phosphorus, or both, in the urine. This is the case in Fanconi's syndrome, in renal tubular acidosis ("hyperchloraemic nephrocalcinosis"), in idiopathic hypercalciuria, and, presumably, in hypophosphataemic glycosuric rickets (Kyle, Meroney, and Freeman, 1954).

Having considered these (and omitting renal glomerular osteodystrophy and the new syndrome of "hypophosphatasia"), we are left with a form of rickets which is unaccompanied by any other outstanding biochemical lesion and which is highly refractory to the effect of vitamin D. This "vitamin-D-resistant rickets or osteomalacia" is frequently hereditary (Pedersen and McCarroll, 1951; Dent and Harris, 1956), and may first appear at any age from birth to adult life. It is uncertain whether the rarer adolescent type of "acquired" resistance (for instance, McCance's (1947) case) is fundamentally different from the childhood disease. The problem is one of basic aetiology. Albright and Reifenstein (1948) claimed that the condition was caused by a resistance to the normal effect of vitamin D on the intestinal absorption of calcium, whereas McCune *et al.* (1943) suggested, and later Dent (1952) strongly supported, the concept of a primary loss of phosphorus via the urine due to a diminished renal tubular reabsorption. Dent and Harris (1956), however, have recently agreed that some defect of intestinal absorption must also be present.

The present paper is written largely in an attempt to add something to the consideration of this problem. A second reason is to consider the mechanism of production of Looser's zones in osteomalacia, which have recently been claimed to be caused by normal arterial pulsation against a weakened bone (LeMay and Blunt, 1949; Steinbach *et al.*, 1954).

Case Report

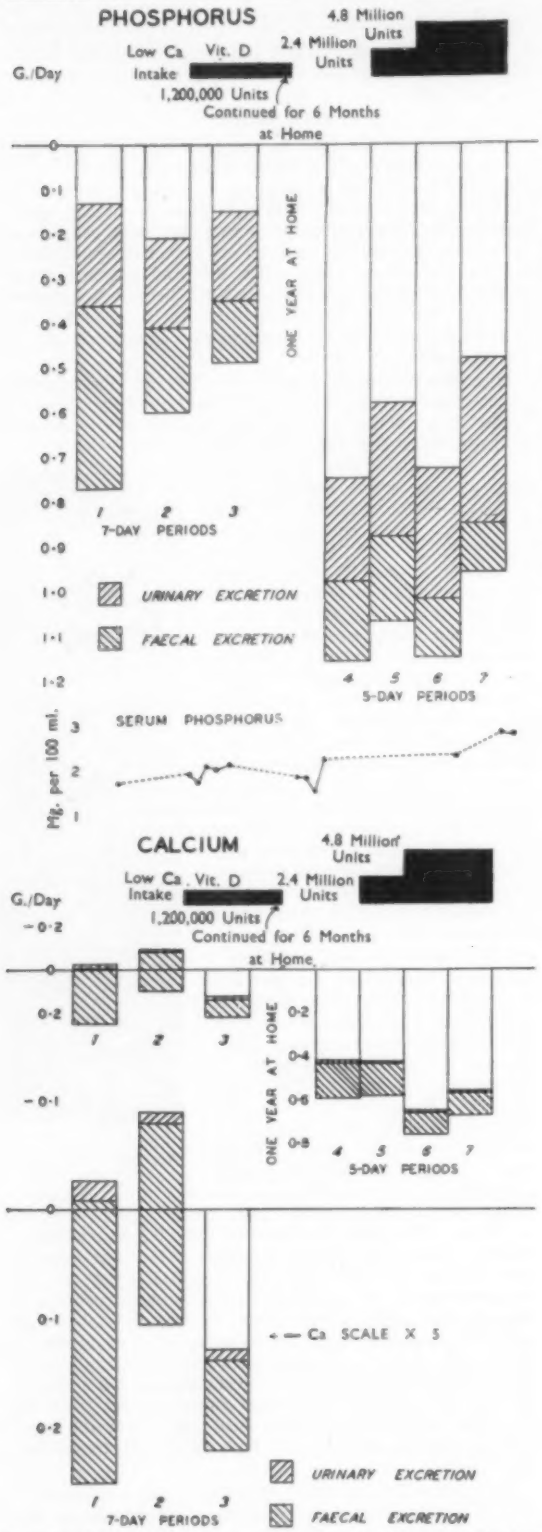
A coloured female aged 32 was referred from the orthopaedic department with inability to walk, painful back, and decalcified bones. Apparently she had always been small, but had walked normally until eight years previously, when, at the age of 24, she developed severe back pain, generalized muscular weakness, and reduced movement of lower limbs. She has not walked since. Her diet and upbringing had not been abnormal and there was no history of intestinal disorder. The menarche occurred at age 16, and menstruation had remained normal and regular. The family history was unreliable.

Inspection revealed a tiny, thin, feeble, short-necked, pigeon-chested, knock-kneed kyphoscoliotic dwarf (Fig. A) of moderate intelligence. She had limitation of movement of spine, hips, and knees and was unable to stand. Her bones were not tender. Secondary sexual characters were well developed. No cystine crystals were seen in the eyes. Weight 52 lb. (23.6 kg.); height 50 in. (1.27 m.), span 52 in. (1.32 m.), upper segment 22 in. (56 cm.), lower segment 28 in. (71 cm.). Haematological and urine examination showed no abnormalities. *X* rays revealed gross generalized decalcification with mollities. The vertebrae were uniformly compressed into biconcave disks. There were multiple near-symmetrical bands and zones of decalcification (Looser's zones) in shoulder girdles, ribs, and pelvis, and one mandible. None of the stigmata of old rickets were present. There were no changes suggestive of hyperparathyroidism, in particular no cortical erosions of the phalanges.

FIG. A.—The patient on her first admission.

Preliminary Investigations.—Serum: calcium 9–11 mg. per 100 ml. (several estimations); inorganic phosphorus 1.2–2.5 mg. per 100 ml. (several estimations); alkaline phosphatase 16–28 units (Shinowara); cholesterol 151 mg. per 100 ml.; sodium 140, potassium 3.4, and chloride 99–106 mEq per litre; carbon dioxide 55 vols.%. Blood urea 17 mg. per 100 ml.; urea clearance 32% (standard) and 33% (maximum) of normal (uncorrected for body size; corrected = 64%). Phenolsulphonphthalein test: 2.5 mg. within 15 minutes (after 6-mg. intravenous dose). Urine calcium less than 20 mg. per day; phosphorus 150–350 mg. per day. Amino-aciduria: no excess of any amino-acid (paper chromatography). Stool rather hard, brown, and microscopically normal. Seven-day fat balance: 99% absorption of 70 g. daily intake. In response to acid feeding (120 gr. ammonium chloride in divided doses within 24 hours) urine *p*H fell from 6.85 to 4.75, urine ammonia rose from 1 to 3.3 mEq per hour, titratable acid rose from 0.1 to 1.0 mEq per hour, and chloride rose from 0.55 to 6.6 mEq per hour.

Diagnosis.—It was apparent from clinical, radiographic, and biochemical evidence that the patient suffered from osteomalacia, which, despite her story, had presumably been active before puberty to account for the shortness of the limbs. (It should be noted that, despite the limbs being relatively longer than the trunk, they are nevertheless abnor-



mally short, being equivalent to a height of only 52–56 in. (1.37–1.42 m.), which would certainly be unusually small for a coloured woman. This makes it seem likely that the disease process had produced stunting of limbs as well as of spine.) As possible causes, steatorrhoea, Fanconi's syndrome, and renal tubular acidosis appeared to have been ruled out by the above-mentioned findings. It seemed most unlikely that the condition could be due to simple vitamin-D lack, but in order to exclude this possibility a trial of five weeks on 10,000 units of calciferol daily was made, but this was without effect on the patient's symptoms or biochemical abnormalities. A diagnosis of acquired vitamin-D-resistant osteomalacia without acidosis or evident renal tubular disease was therefore made.

Second Admission (one year later).—The patient received 1.2 million units of calciferol intramuscularly daily for about six months after her discharge from hospital. She had remained stronger and brighter, was pain-free, and was actively disporting herself with one crutch, despite the six months' discontinuance of vitamin D. In the ward her weight rose from 52 to 55 lb. (23.6 to 25.0 kg.).

Notwithstanding her clinical improvement, the radiological and biochemical findings were virtually the same as on the first admission; in particular, the Looser's zones were unhealed and biochemical osteomalacia was still present. On admission the serum phosphorus was 1.5 mg. per 100 ml. and the alkaline phosphatase 18 Shinowara units.

Special Metabolic Investigations

A. Metabolic Balance Studies (Fig. B)

During the patient's first admission, only three seven-day balance periods were possible. These studies were carried out after the method of Reifenstein *et al.* (1945) and are so charted. Calcium and phosphorus were determined in aliquots of the diet, and the results were checked by calculation from food tables. After a change of diet two weeks were allowed for equilibration before a fresh balance was started.

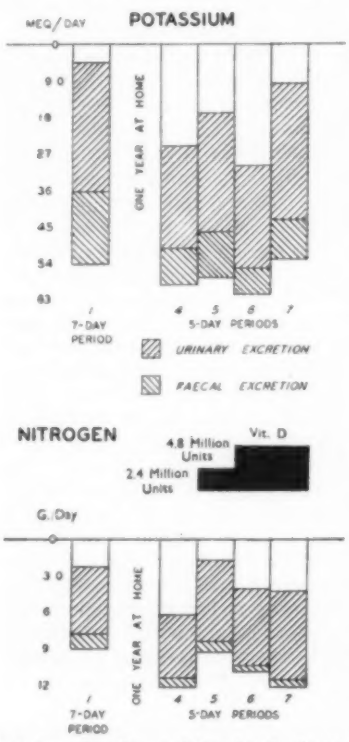


FIG. B.—Metabolic balance studies. Total intake is plotted downwards from baseline, and faecal and urinary components are charted from bottom of intake. Thus a white portion below baseline indicates a positive balance while if column rises above baseline there is a negative balance. The calcium balances 1, 2, and 3 are repeated below the other calcium balances on a scale five times as large. Note excessive stool calcium on low calcium intake, effect of vitamin D in lowering stool calcium and phosphorus, and eventual raising of serum phosphorus while on 4.8 million units of calciferol per day. For further discussion see text.

First Period.—During the first balance the patient's diet was of her own choice. We were surprised to find how low in calcium this was (little more than 200 mg. per day); however, this sort of calcium intake is commonly found in the underprivileged classes in South Africa, whereas osteomalacia is not. On this intake she was almost in balance for calcium. The retention of phosphate may well have been related to the physiotherapy and muscle training she received the whole time she was in hospital, during which she gained some 4½ lb. (2.04

FIG. 1.—Aortic thrombosis just below level of renal arteries. Note small subcostal arteries, atheromatous stenosis of left renal artery, and inferior mesenteric artery supplied by left colic branch of superior mesenteric artery.

FIG. 2.—Aortic thrombosis below inferior mesenteric artery just above bifurcation of aorta.

FIG. 3.—Aortic thrombosis at origin of inferior mesenteric artery. (Note tapering of aorta.)

FIG. 4.—Aortic thrombosis just below renal arteries.

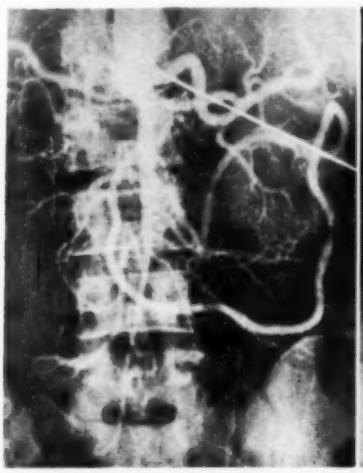


FIG. 5.—Aortic thrombosis at level of renal arteries with involvement of one renal artery. Note that inferior mesenteric artery is supplied by left colic branch of superior mesenteric. There is a left nephrogram but no right nephrogram.

FIG. 6.—Aortic thrombosis above level of inferior mesenteric artery. As in Fig. 1, latter is supplied by hypertrophied left colic branch of superior mesenteric artery. Lower limit of block is in common iliac artery on right, but in femoral artery on left. Left internal iliac artery, however, is filled from collaterals.

FIG. 7.—Lower limits of aortic block shown on serial films. This is same case as Fig. 2, and demonstrates in nephrogram phase the associated horseshoe kidney.

FIG. 8.—Aortic stenosis due to atheroma just above bifurcation. Operative clips are from a previous sympathectomy. At operation condition had progressed to complete thrombosis of aorta.

N. K. CHANDA: LIVER IN KWASHIORKOR

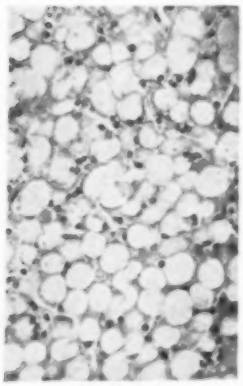


FIG. 1.—Section of liver of Group I, Subgroup A, showing extreme fatty change of liver cells; the sinusoids are collapsed and empty. (H. and E. ×255.)

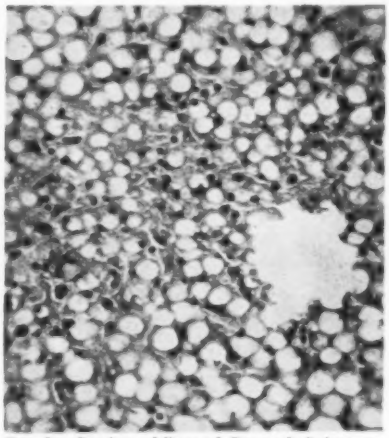


FIG. 2.—Section of liver of Group I, Subgroup C, showing fatty change in liver cells and dilatation of sinusoids; central vein also much dilated. (H. and E. ×144.)

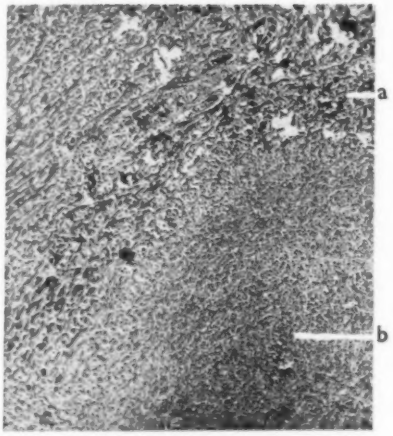


FIG. 3.—Section of liver showing (*a*) few hepatic cords in upper half; (*b*) necrosis of hepatic cells and infiltration with neutrophils and histiocytes in lower half. (H. and E. ×70.)

FIG. 4

FIG. 5

FIG. 6

FIG. 4.—Case 1. Section of liver showing: fibrous tissue spreading from portal tracts, resulting in monolobular cirrhosis; liver cells with fatty change at periphery of lobule; and dilatation of sinusoids in centre of lobule. (H. and E. ×88.)

FIG. 5.—Case 4. Section of liver showing monolobular distribution of fibrosis. Hepatic lobules show dilatation of central vein and sinusoids in central and mid-zonal areas, fatty change in liver cells in peripheral zone, and lymphocytic infiltration and biliary proliferation of fibrous tissue. (H. and E. ×44.)

FIG. 6.—Section of liver showing necrosis of hepatic cells and monolobular distribution of fibrosis. (H. and E. ×44.)

J. R. COLLEY *ET AL.*: RENAL LESION IN ANGIOKERATOMA CORPORIS DIFFUSUM

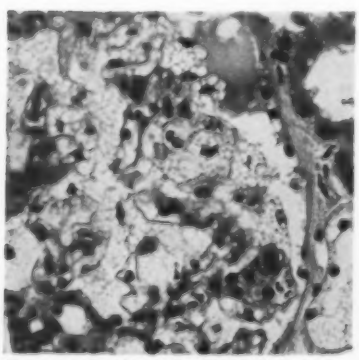


FIG. 1.—Portion of glomerulus from Case 2 showing "honeycomb" appearance due to distension and vacuolation of epithelial cells of tuft. An adjoining distal tubule cell shows the same appearance. (H. and E. ×305.)

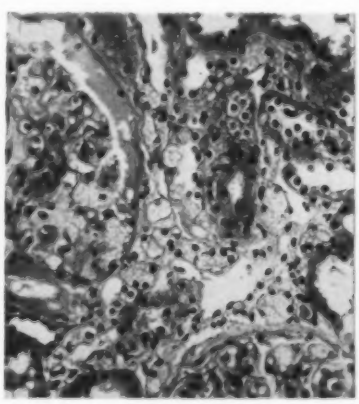


FIG. 2.—"Honeycomb" glomeruli with similar vacuolation of adjacent tubules. (H. and E. ×170.)

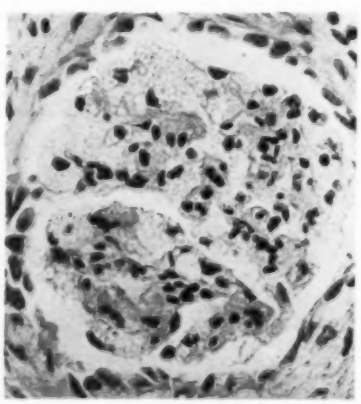


FIG. 3.—"Honeycomb" glomerulus from Case 3 with early periglomerular fibrosis. (H. and E. ×305.)

W. P. U. JACKSON *ET AL.*: VITAMIN-D-RESISTANT OSTEOMALACIA

FIG. 1.—Radiograph of pelvis. Note wide symmetrical Looser's zones in pubic and ischiopubic rami, and narrow zones running from angle of brim of pelvis.

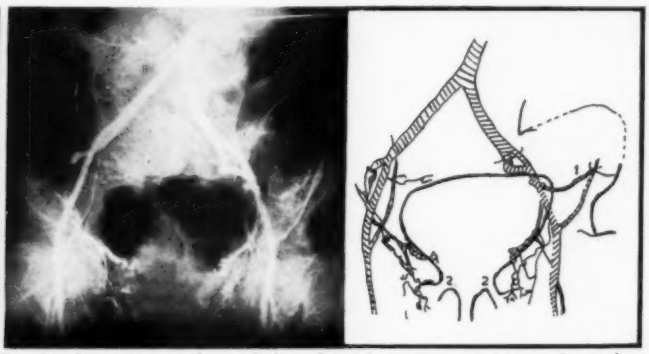


FIG. 2.—Aortogram to show relation of arteries to Looser's zones. In tracing, continuous line indicates pelvic outline. Note that superior gluteal artery (1) appears to be in fairly close superimposition over one zone, whereas no arteries are to be found near wide pubic zones (2).

FIG. 3

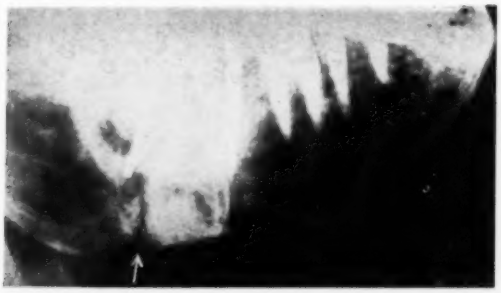


FIG. 4.—Looser's zone close to last molar tooth. Incidentally lamina dura around teeth has largely disappeared.

FIG. 3.—Left shoulder girdle. Note Looser's zones at surgical neck of humerus, in scapula close to glenoid cavity, and traversing greater wing from lateral border.

M. RIDDLE *ET AL.*: NEPHROTIC SYNDROME COMPLICATING MERCURIAL DIURETIC THERAPY

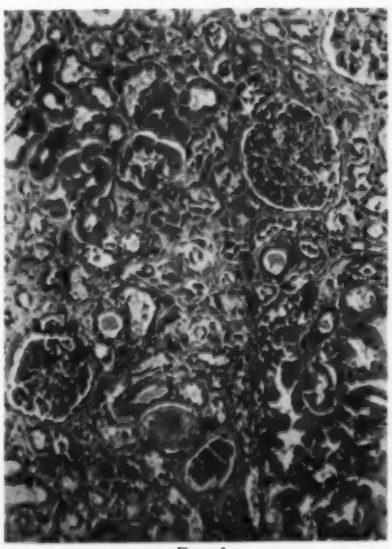


FIG. 1

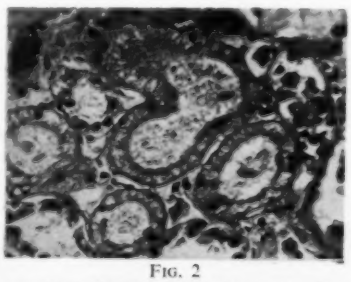


FIG. 2

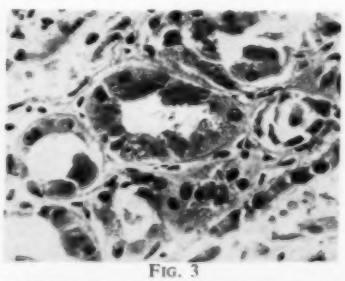


FIG. 3

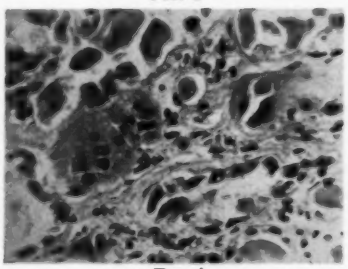


FIG. 4

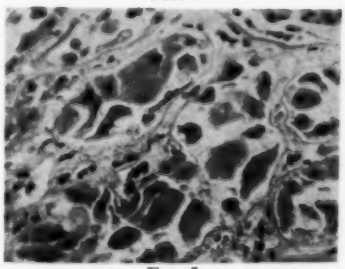


FIG. 5

FIG. 1.—Epithelial degeneration and necrosis in proximal convoluted tubules (top left and bottom right), with regeneration of tubular epithelium (centre). (H. and E. ×75.)

FIG. 2.—Proximal convoluted tubules showing epithelial necrosis with vacuolation of cytoplasm and nuclear pyknosis. Brush borders are preserved. Cellular debris in tubular lumina. (H. and E. ×200.)

FIG. 3.—Proximal convoluted tubules showing hyaline droplet degeneration. (H. and E. ×200.)

FIG. 4.—Tubules showing epithelial regeneration. A binucleate cell is present (lower centre). (H. and E. ×200.)

FIG. 5.—Tubules showing regeneration. A mitotic figure can be seen near top left-hand corner. (H. and E. ×200.)

C. S. DARKE *ET AL.*: LARYNGEAL STRIDOR IN RHEUMATOID ARTHRITIS

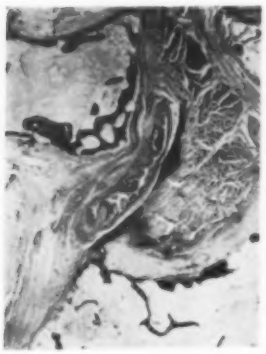


FIG. 1.—Longitudinal section of larynx (Case 1), showing thickened synovial membrane of cricoarytenoid joint. (×6.)

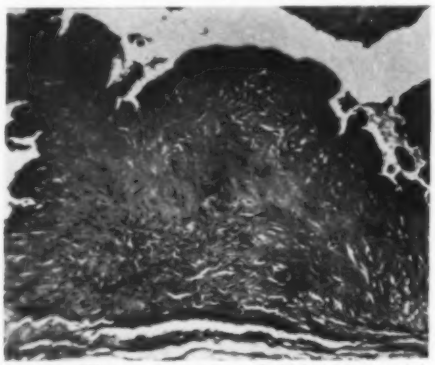


FIG. 2.—Higher power view of thickened synovial membrane of cricoarytenoid joint (Case 1), showing chronic inflammatory cells. (×98.)

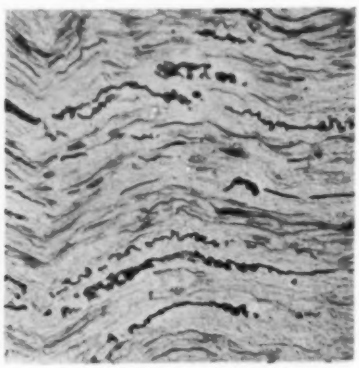


FIG. 3.—Lower part of left recurrent laryngeal nerve (Case 1), showing degenerate tortuous axis cylinders. (Silver stain. ×306.)

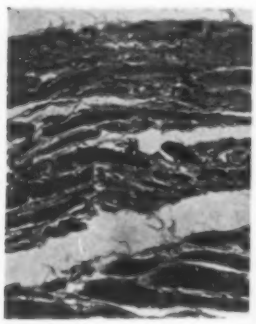


FIG. 4.—Longitudinal section of posterior cricoarytenoideus muscle (Case 3), showing neural atrophy. Bundles of atrophic fibres with increased numbers of nuclei are separated by larger intact fibres. (×86.)

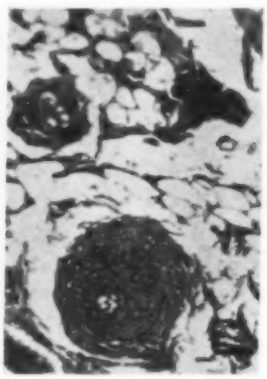


FIG. 5.—Vasa nervorum in left vagus (Case 3), showing severe intimal proliferation with reduction in size of lumen. (×60.)

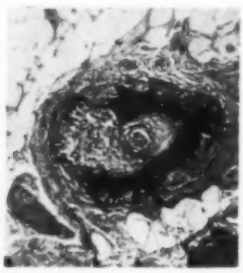


FIG. 6.—Calcification in intima and internal elastic lamina of artery supplying upper part of left recurrent laryngeal nerve (Case 3). Two minute channels are present in centre. (×56.)

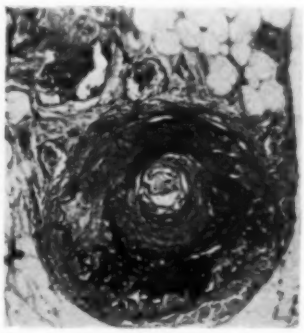


FIG. 7.—Similar calcification in vasa nervorum in lower part of left recurrent laryngeal nerve (Case 3). (×56.)

E. CLARKE: CERVICAL MYELOPATHY PRESENTING AS PERIPHERAL NEUROPATHY

FIG. 1.—Case 1. Myelogram showing anterior and posterior filling defects in cervical region.

FIG. 2.—Case 2. Myelogram showing anterior and posterior filling defects in cervical region.

J. A. WILLIAMS: AN UNUSUAL SITE FOR GRAVITATIONAL ULCERS

An apparently normal femoral vein has "concertinaed" following a femoral osteotomy. There is 2 in. (5 cm.) of shortening.

kg.) in weight. The urine phosphorus, however, is noticeably low in comparison with the high faecal level.

Second Period.—On a low calcium intake of only 100 mg. per day the negative balance of 100 mg. was almost entirely caused by the faecal loss being higher than the intake. This apparent paradox is possible if a proportion of the calcium excreted into the gut via the bile and other intestinal secretions is not reabsorbed.

Third Period.—This balance study was performed after the patient had already been on 1.2 million units of calciferol daily by injection for seven days. Her calcium intake was not increased over her original chosen amount, but there is now a positive retention of this mineral, due to reduction in faecal loss. There is also diminished faecal phosphate loss, but her diet during this balance period contained considerably less total phosphorus, so that the significance of this is difficult to assess. The second and third balance periods were each started three days after a phosphate infusion experiment.

Fourth Period.—The later balance studies on her return visit showed a remarkable retention of all elements examined. With regard to the calcium and the equivalent phosphate moiety, we wondered whether the calciferol received some months previously was still active in Period 4, having waited, so to speak, for a higher intake of minerals upon which it could work. The home intake of these was undoubtedly low.* It is to be noted that the faecal calcium and phosphorus are both considerably lower in Period 4 than in Period 1, despite a far higher intake.

Fifth, Sixth, and Seventh Periods.—The calciferol in Period 5 made no apparent change to the absorption. In Periods 6 and 7 the enormously high dose of nearly 5 million units daily produced a further fall in faecal calcium and phosphorus, indicating increased absorption. Some increase in urinary phosphorus has occurred, coincidental with a rise in serum phosphate. The retention of phosphorus, nitrogen, and potassium was accompanied by a weight gain of 2 lb. (0.907 kg.) over the period of balance study (15 days).

Comment on Balance Studies.—The absorption of calcium and phosphorus before treatment is poor. Vitamin D (as calciferol) in very large doses increases the absorption of these minerals. The effect of the first intensive course of vitamin D is still apparent after six months.

B. Effect of Parathyroid Extract (Ellsworth–Howard Test)

Parathyroid extract ("parathormone") of proved urine-phosphate-raising potency, was injected intravenously in the high dosage of 1,000 *U.S.P.* units after three control periods of one hour each. The urine was collected by catheter. There was no significant change in the urinary phosphate over the next three hours, nor in the serum level of calcium. The urine calcium, however, showed a distinct rise (Table I), and the serum phosphorus also became higher.

TABLE I.—*Effect of Parathyroid Extract* (1,000 *Units Intravenously*)

Time	Urine		Serum	
	Phosphorus (mg./hour)	Calcium (mg./hour)	Phosphorus (mg./100 ml.)	Calcium (mg./100 ml.)
8–9 a.m. ..	8·0	0·3		
9–10 ,, ...	10·4	1·0	1·24	9·7
10–11 ,, ...	Some of this specimen was lost			
	1,000 *U.S P.* units "parathormone"			
11 a.m.–12 noon ..	9·5	2·5		
12–1 p.m.	9·4	1·7	1·83	9·5
1–2 ,, ...	8·3	0·4		

*Gross errors in analyses are unlikely. The dietary intake was checked by estimation from tables. The low excretion in the case of calcium is conditioned by a low faecal figure, while in the case of nitrogen and potassium the urine is the important channel of excretion. Calculations were double-checked and each balance treated entirely separately.

On the second admission 400 units of parathormone were given intramuscularly daily for four days. There was a delayed (fourth-day) rise in urinary calcium and phosphorus. The calcium actually increased from 1–4 mg. to 64 mg. per 24 hours.

C. Renal Handling of Phosphate and the Effect of Infused Calcium

(1) Accurate investigation of the Tm (maximum tubular reabsorption) for phosphate (TmP) was carried out in the experiment in which calcium gluconate was infused. (*Inter alia* we desired to see whether intravenous injection of calcium affected the TmP.) The method was as follows. The patient was maintained on a diet of constant calcium and phosphorus content for several days before the experiment, which was done in the fasting state with the patient supine. A priming dose of inulin and buffered sodium phosphate at *p*H 7.4 was administered intravenously to raise serum levels of the inulin and inorganic phosphorus to approximately 40 mg. and 10 mg. per 100 ml. respectively, and these substances were infused at a constant rate thereafter to maintain these serum levels for the first 3½ hours of the experiment. Urine samples were obtained at accurately timed 20-minute intervals during the first 3½ hours by bladder washout with distilled water and air, and subsequently at two-hourly intervals through an indwelling catheter for 24 hours. Blood samples were taken without anticoagulant 2½ minutes before the midpoint of each 20-minute period. After two 20-minute periods 280 mg. of calcium (as 30 ml. of 10% calcium gluconate) was infused into a leg vein over a period of 20 minutes. We attempted to maintain the patient in a state of constant hydration, enough fluid being given by mouth to maintain a constant total intake.

Results are given in Table II. There was a mean inulin clearance of 76.5 mg. per minute which was not obviously affected by intravenous calcium. The serum phosphate was

TABLE II.—*Results of Intravenous Calcium and Phosphate Infusion*

Period	G.F.R. (Inulin Clearance)	Serum Ca (mg./100 ml.)	Serum P (mg./100 ml.	Urine Ca (mg./spec.)	P Load (mg./min.)	Urine P (mg./min.)	Tubular reabs (Tmp). (mg./min.)	$\frac{Tm_P \times 100}{G.F.R.}$
Blank		9·1	1·7					
1	70	8·0	8·5	0·6	6·0	3·5	2·5	3·6*
2	78	7·4	8·0	0·5	6·3	4·2	2·1	2·7
	Calcium infusion starts							
3	88	7·4	7·5	0·4	6·8	4·7	2·0	2·3
4	87	8·6	7·2	1·0	6·3	4·2	2·1	2·5
	Calcium infusion ends							
5	77	9·6	7·2	1·2	5·6	3·6	2·0	2·6
6	65	8·8	7·0	0·6	4·6	2·9	1·7	2·6
7	80	7·9	6·8	0·5	5·5	3·2	2·2	2·8
8	72	7·7	6·7	0·4	4·8	3·2	1·6	2·3
9	73	7·1	6·7	0·4	4·9	3·2	1·6	2·2
10	74	7·4	6·6	0·3	4·8	2·9	2·0	2·7

* TmP for the first period is always high and should be disregarded.

raised from 1.7 to 8 mg. per 100 ml. by the priming dose, but it fell gradually during the infusion. At serum phosphorus levels considerably higher than the mean threshold the TmP remained at some 2 mg. per minute, which means that some 2.5 mg. of phosphorus was reabsorbed per minute per 100 ml. of glomerular filtrate. This value was not affected by calcium infusion.

The final finding of this experiment refers to the rapid withdrawal from the circulation and the retention of the infused calcium. It may be seen from Table II that the serum calcium was depressed by the phosphate infusion, and rose only slightly and transiently after the calcium infusion, although the calculated elevation was to 14 mg. Furthermore, almost 100% of the injected 280 mg. was retained,

there being a total extra-urinary excretion of some 2–3 mg. only during the test period. (A similar depression of serum calcium by phosphate infusion was seen on another occasion when the TmP was measured.)

(2) On the patient's second admission the TmP was again measured by the same method. Calcium was not infused. The serum phosphorus was maintained at 6 mg. per 100 ml. and the percentage of reabsorption of the glomerular load was around 50% (indicating that the Tm had been exceeded). The mean TmP was found to be 2.3 mg. per minute—that is, 2.8 mg. per 100 ml. of glomerular filtrate. This was a little higher than the previous level, but still below our normal range. (Our figure for normal values for TmP, taking the mean of 48 investigations in different subjects, is 4.05 ± 0.7 mg. per 100 ml. filtrate formed.)

(3) A calcium infusion experiment was again performed, this time without concomitant intravenous phosphate. Because of the rapid withdrawal of extra calcium from the blood stream found in the first experiment, a total of 930 mg. of calcium was infused, some three times the calculated amount necessary for raising the serum calcium to 14 mg. per 100 ml. In this experiment the calcium was infused at an increasing rate from the beginning of the first period until the end (of Period 9). As may be seen from Table III: (*a*) the serum calcium rose from 10.1 to 14.1 mg. per

TABLE III.—*Results of Second Intravenous Calcium Infusion*

Period	Minute Vol. (ml.)	G.F.R.	Serum Ca (mg./100 ml.)	Serum P (mg. 100 ml.)	Urine Ca mg. spec.	P. Load mg. min.	Urine P mg. min.	TmP	TmP × 100 / G.F.R.
Blank			10·2						
1	10·0	70	10·5	1·6	0·4	1·13	0·09	1·04	1·49
2	9·8	62	10·8	1·7	0·5	1·03	0·08	0·95	1·53
3	11·0	63	10·7	1·7	1·9	1·07	0·09	0·98	1·56
4	12·2	65	10·7	2·1	3·8	1·35	0·08	1·27	1·95
5	8·5	58	11·2	2·0	4·8	1·17	0·07	1·10	1·90
6	9·0	69	11·8	2·4	9·5	1·64	0·09	1·55	2·25
7	8·8	67	13·0	2·6	13·8	1·71	0·10	1·61	2·40
8	8·3	56	13·5	2·4	15·0	1·45	0·80	1·37	2·45
9	9·4	57	14·1	2·4	11·0 51·0*	1·35	0·07	1·28	2·25

* Remainder of 24-hour period. Total (24 hours) = 112 mg.

100 ml.; (*b*) the serum phosphorus rose from 1.6 mg. to a maximum of 2.6 mg.; (*c*) there was no appreciable change in urine phosphorus; (*d*) there was no appreciable change in glomerular filtration rate; (*e*) despite some increase in phosphate load and minute tubular reabsorption, the latter never reached the previously calculated Tm, so that no change in this function could be measured; (*f*) no increase in minute volume was produced; (*g*) some 89% of the infused calcium was retained (apparently permanently).

Comment on Results of Infusion Experiments.—(1) The low capacity of the renal tubules to reabsorb phosphorus might be primary tubular defect or an effect of secondary parathyroid overactivity (see below). (2) Calcium gluconate (or laevulinate) infused into normal subjects always produces a diuresis in our experience (18 subjects). It failed to have this effect in the present case. (3) The remarkable retention of the infused calcium and its rapid removal from the circulation indicate that the bones were avid for this mineral. Kyle, Schaaf, and Erdman (1954) found similar retention in other varieties of osteomalacia, but in the vitamin-resistant case of Segar *et al.* (1956) the bones appeared incapable of extracting the infused calcium, so that 75% was recovered in the urine. (4) The rise in serum phosphorus in the third experiment was unaccompanied by any change in urine phosphorus, and must therefore be a result of internal redistribution of phosphate or, less likely, of sudden absorption from the gut. In both normal and hypoparathyroid subjects it is also necessary to invoke a shift of phosphorus from intracellular to extracellular fluid compartment to explain the phenomena following calcium infusion.

D. Effect of Calciferol on Phosphate Metabolism

(1) During the patient's first admission, after she had been treated with parenteral calciferol in doses of 600,000 units for 10 days followed by 1,200,000 units daily for four days, the TmP was again measured. The infused phosphate raised the serum level to around 6 mg. per 100 ml., and, since only 27% of the filtered load was reabsorbed, it may be presumed that the maximum reabsorptive capacity of the tubules had been exceeded. The TmP was unchanged by the calciferol at 1.7 mg. per minute, or, correcting for glomerular filtration rate (G.F.R.), 2.5 mg. reabsorbed per 100 ml. of filtrate formed. It is noteworthy that our estimations of the capacity of the tubules of the patient to reabsorb phosphorus are remarkably constant (2.5–2.8) when expressed as mg. reabsorbed per 100 ml. of glomerular filtrate formed.*

We conclude, therefore, that the low capacity of the patient's tubules to reabsorb phosphorus was unaffected by intravenous calcium or by calciferol in the dose given. Because of the length of time which may be required for the full effect of calciferol to become apparent, it is possible that a change in tubular reabsorption capacity would have been found had the test been repeated after longer treatment.

(2) In the second admission, calciferol in doses of 4.8 million units daily led to a rise in serum phosphorus to normal levels (Fig. B). Albright and Reifenstein (1948, p. 127) made similar observations in a case of resistant osteomalacia, and concluded that the raised serum phosphate was caused by a reduction in parathyroid activity consequent upon a raising of serum calcium. However, neither their nor our balance charts indicate any fall in urine phosphorus, which would have to be the first happening on this line of reasoning.

E. Effect of Calciferol on the Patient's Disease

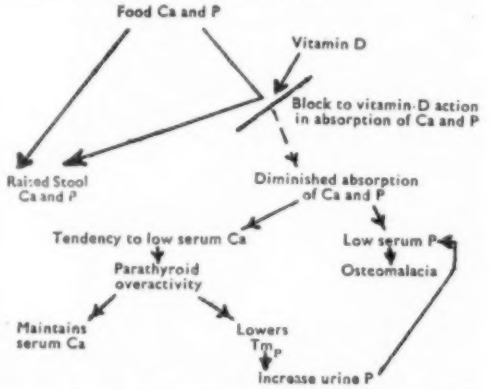
During the first admission calciferol in the large doses mentioned above had no discernible effect on serum or urinary calcium or phosphorus: there was no clinical change or alteration in weight after 17 days on 1.2 million units. On the other hand, the increased absorption and retention of calcium shown by balance study suggested that other good effects would later accrue. In fact, as was seen a year later, a clinical improvement had continued. Nevertheless nearly 5 million units of calciferol daily was necessary before elevation of serum phosphorus occurred, while even on this dose there was no rise in serum or urinary calcium.

Discussion

Pathogenesis

In order to state the problem of pathogenesis or resistant osteomalacia the rival theories are shown diagrammatically.

(1) "Albright Theory" (intestinal block).



*It may be noted that this method of expression of TmP automatically corrects both for body size and for incomplete bladder emptying.

On this theory the healing effect of massive doses of vitamin D is produced by overcoming the block. The parathyroid activity should then return to normal.

(2) "McCune–Dent Theory" (low phosphate threshold).

Low TmP
↓
Increased urine P
↓
Low serum P
↓
Osteomalacia

On this theory the healing effect of massive doses of vitamin D is more complicated and may be partly due to the "forcing-in" effect of calcium and phosphorus through the gut. Dent believes that vitamin D in large doses actually raises the TmP; this effect would plainly be curative.

Consistent with either theory are: (1) Low TmP (about 1.0 mg. per minute in the case of Segar *et al.* (1956); about 2.0 mg. per minute in our case). (2) Curative effect of massive dosage of vitamin D. (3) Failure of phosphate diuresis after parathyroid extract. On the first theory the tubules would already be responding, possibly maximally, to endogenous parathyroid hormone, while on the second theory the abnormally low TmP might well be resistant to further depression.

In favour of the first theory: (1) Secondary hyperparathyroidism with hyperplasia has been found on exploration of parathyroid glands (Linder and Vadas, 1931; Highman and Hamilton, 1936; Albright *et al.*, 1937). (2) Poor absorption of calcium and phosphorus has been found by Albright and Reifenstein (1948) and by Saville *et al.* (1955) and is clearly shown in the balance data of our case. (3) Intravenous calcium would be expected to raise the serum calcium, to depress parathyroid activity, and so raise the depressed tubular reabsorption of phosphorus. In our case the phosphate load presented to the tubules during the second calcium infusion never exceeded the low maximal reabsorption, so we cannot draw any conclusions along these lines. In the case of Segar *et al.* (1956) the TmP was almost doubled by the calcium infusion. (4) In our case calciferol increased calcium absorption and produced symptomatic improvement without any change in tubular reabsorption of phosphate. (5) Some, but not all, cases (including ours) have shown a lowered urinary calcium with a normal serum level. By analogy with ordinary vitamin-D-lack rickets this is not unexpected.

Against the first theory: (1) Not all cases have low urine calcium (McCance, 1947; Albright and Reifenstein, 1948; Segar *et al.*, 1956), although this is probably invariable in ordinary rickets. (2) No cases with a low serum calcium seem to have been reported; this again is unlike ordinary rickets. (3) The bones show no features of osteitis fibrosa, as would be expected with secondary hyperparathyroidism. This comment applies also to ordinary rickets. (4) The occurrence of glycosuria in some cases cannot be explained.

In favour of the second theory: (1) There is a consistently normal serum calcium. (2) There is an analogy with other functional renal tubular disorders (for example, Fanconi syndrome). (3) The glycosuria in some cases is easily explicable on the basis of associated tubular dysfunction.

Against the second theory: (1) The low urine calcium usually found is inexplicable. (2) There is no apparent reason for parathyroid hyperplasia. (3) Since intestinal absorption is unimpaired, there appears to be no explanation for the high faecal calcium and phosphorus. (This fact has been admitted by Dent and Harris, 1956.) (4) Intravenous calcium would not be expected to alter an abnormally depressed tubular reabsorption of phosphate (which clearly happened in the case of Segar *et al.*).

It is plain that there are arguments in favour of both theories. Certainly it should not be assumed (as appears to be done by British authors recently: Rose, 1956) that the renal tubular theory is correct. There is perhaps more in favour of the Albright theory.

We should like to suggest another possibility—namely, that there is more than one variety of resistant osteomalacia, with more than one basic pathogenesis. In favour of this idea are: (1) The irreconcilability of the arguments in favour of either *single* theory. (2) The strange finding of very low urinary calcium in some cases (as in ordinary rickets) and of normal or even high urinary calcium in others. In this connexion, a raised urinary calcium secretion has been found in the *glycosuric* hypophosphataemic group (Anderson *et al.*, 1952), suggesting a syndrome with multiple defects of tubular function (Jackson and Linder, 1953), of which one may be a diminished reabsorption of filtered calcium, reminiscent of "idiopathic hypercalciuria." (3) The case reported by Segar and co-workers, in which neither theory seems to afford adequate explanation. This patient was unable to retain either absorbed or infused calcium, so that large doses of vitamin D, although increasing calcium absorption, were not curative. In this case there appears to have been an additional "internal" or skeletal defect. (4) Dent (Dent and Harris, 1956) claims certain distinctions between the childhood and later types of the disorder, in particular an excess of urinary glycine in the adolescent cases he has examined. (This was not present in our case.)

Diagnosis

The present patient seems to have a primary defect in intestinal absorption. Thus she has a defective absorption shown on balance studies, correctable by massive doses of calciferol. She also shows a lowered tubular reabsorptive capacity for phosphate, but whether this is a primary defect or secondary to parathyroid activity or other agency we cannot say. We therefore label her condition as acquired vitamin-D-resistant osteomalacia with intestinal block and reduced tubular reabsorption of phosphate.

Pathogenesis of Looser's Zones

Looser's zones are bilaterally near-symmetrical bands of uncalcified tissue (*Umbauzonen*) which occur particularly in the ribs, shoulder girdle, pelvis, upper end of femur, tibia, and fibula. They are probably pathognomonic of osteomalacia, and may appear even when there is no radiographic evidence of demineralization (Milkman's syndrome). LeMay and Blunt (1949) found by anatomical dissection that the zones coincided with sites in which bones came into close connexion with arteries, and suggested that they were caused by continuous pulsation beating against a softened cortex. Steinbach and co-workers (1954) claimed to confirm this by arteriography, showing some of the pseudo-fractures to be in proximity to an abnormal obturator artery in one case. (We are, however, not at all impressed with the relation of the lower pair of zones to the artery as shown in these authors' Fig. 6.)

After consultation with Dr. E. L. Allen, Professor of Orthopaedic Surgery, Dr. R. H. Goetz, Professor of Experimental Surgery, and Dr. E. N. Keen, of the Department of Anatomy, we should like to criticize this theory on the following grounds: (1) it is difficult to explain certain of the zones which seem to be remote from traversing arteries, as in the ischio-pubic ramus and the ribs; and (2) in other sites where arteries wrap themselves directly around bone Looser's areas are not usually found, as in relation to the radial artery, the external iliac artery, and the facial artery (in the mandible). Professor Goetz, with great difficulty, performed transaortic arteriography in the present case, as shown in Fig. 2 of the Special Plate. Comparison of this with the straight radiograph (Special Plate, Fig. 1) indicates that the superior gluteal artery appears closely superimposed upon a zone, at least on the left side. However, the gluteus minimus muscle lies between the artery and the bone. The wide zones in the pubic ramus have no arterial relation. Turning to the shoulder girdle, the circuitous zone on the scapula (Special Plate, Fig. 3, arrow) is very suggestive of an arterial course and might be imagined as being in relation to the circumflex scapular artery. Dr. Keen, however, assures us that the zone is considerably superior

to the usual position of this artery. The zones on the surgical necks of the humeri again appear to us to be far too high to coincide with the normal course of the circumflex humeral arteries. Other wider zones in the shoulder region do not appear to have any possible arterial relationship. The zone in the mandible (Special Plate, Fig. 4), opposite the second molar tooth, is nearly half an inch (12.5 mm.) distant from the facial artery, as judged by the site of its pulsation. We therefore suggest that the arterial origin of Looser's zones is, at the most, only partly true, and does not appear applicable even to the narrower and tortuous zones, while some other explanation is certainly needed for the wide transverse bands.

Summary

The place of so-called "vitamin-D-resistant rickets and osteomalacia" is considered, followed by the report of the case of a woman aged 32 with osteomalacia and Milkman's syndrome. Other causes for osteomalacia were ruled out, and various metabolic investigations were then performed. Balance studies showed a high faecal calcium and phosphorus, phosphorus infusion studies showed a low tubular maximal reabsorption of phosphorus (high phosphate clearance), and calcium infusion studies showed several points of difference from the normal. The bones gave evidence of great avidity for calcium. The response to parathyroid extract was slight, delayed, and affected calcium more than phosphorus metabolism.

The effect of calciferol given parenterally in large doses was examined. On 1.2 million units per day the calcium and phosphorus absorption increased, but it was not until a dose of 4.8 million units daily was used that the serum phosphorus showed any rise. No toxic effects were seen on this dose after 14 days. The smaller dose of 1.2 million units had no effect on the tubular reabsorption of phosphate.

Finally the mechanism of production of Looser's zones is considered. The relation of some of the zones to arteries was studied by means of contrast medium introduced into the aorta. It is concluded that the zones are not in close connexion with pulsating blood vessels.

APPENDIX

The main chemical methods used were as follows. Serum calcium: Greenblatt and Hartman (1951); serum and urinary inorganic phosphate: King (1951); urinary, faecal, and food calcium: Jackson and Irwin (1958); nitrogen: micro-Kjeldahl; inulin: Roe *et al.* (1949); potassium: flame photometer (Jackson and Irwin, 1958).

The results of balance studies have been given in charts rather than tables, in order to conserve space. The exact figures may be obtained from the authors on request.

We are pleased to express our thanks to Professor J. F. Brock and Professor F. Forman for their interest and advice; to those who helped with the section concerning Looser's zones (particularly Professor R. Goetz); to Mr. B. Todt for the photographs; to the interns, the nursing and technical staff concerned, and to the dietitians. We gratefully acknowledge grants from the Council for Scientific and Industrial Research of South Africa and from the University of Capetown Staff Research Fund, which covered the expenses entailed.

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THE NEPHROTIC SYNDROME COMPLICATING MERCURIAL DIURETIC THERAPY

BY

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[WITH SPECIAL PLATE]

Mercurial diuretics are powerful weapons in the treatment of congestive heart failure. Their proper use can maintain reasonable health and activity for long periods in individuals who would otherwise be seriously disabled. It is well recognized, however, that these drugs are potentially dangerous on account of their action on the renal tubular epithelium. For this reason they are usually withheld from patients with established renal disease, though Gold *et al.* (1947) state that a mercurial diuretic may be given to patients with congestive failure "regardless of the state of the kidneys."

Isolated reports of the nephrotic syndrome occurring after prolonged administration of mercurial diuretics have appeared (Waife and Pratt, 1946; Derow and Wolff, 1947; Bruno, 1948; Siegel and Friedman, 1949; Preedy and Russell, 1953; Munck and Nissen, 1956), but we are not entirely satisfied that the renal tubular damage in all these cases should be attributed to mercury. In the patients reported by Bruno (1948) and by Siegel and Friedman (1949) the clinical and pathological findings suggest that the renal tubules had been damaged by mercury, but diabetic intercapillary glomerulosclerosis (Kimmelstiel–Wilson disease) was also present. Munck and Nissen (1956) describe the nephrotic syndrome occurring in four patients who had received mercurial diuretics, but very limited pathological data are given, and in the one case which came to necropsy the kidneys were normal. The case reported by Derow and Wolff (1947) is acceptable on clinical grounds, but post-mortem examination was not performed and there is therefore no histological evidence. In the cases reported by Waife and Pratt (1946) and by Preedy and Russell (1953), on the other hand, there is

little doubt that the nephrotic syndrome was due to mercury. In these patients there was no preceding kidney disease, and the histological findings, of lesions confined to the renal tubules, are strongly suggestive of mercurial damage.

In the past three years we have seen five cases of the nephrotic syndrome, three of them fatal, which appeared to follow the use of mercurial diuretics. We believe that this syndrome is a definite risk in long-term mercurial diuretic therapy, and that it may be more frequent than has hitherto been supposed.

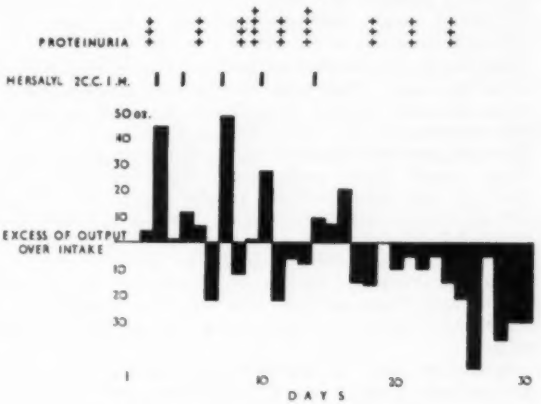
Case Reports

Case 1.—A woman aged 67 years with degenerative heart disease. When first seen she had received weekly injections of mersalyl for three years and was known to have had a low urinary output and proteinuria for three months. There was generalized oedema, but the jugular venous pressure was normal. The important biochemical findings (see Table) were heavy proteinuria, hypoalbuminaemia, and hypercholesterolaemia. Treatment was ineffective; the blood urea rose from 53 to 135 mg. per 100 ml., and the patient died 19 days after admission to hospital.

Case 2.—A woman aged 80 years with hypertensive heart disease. Four years before death she was treated in hospital for congestive cardiac failure. Renal function at that time was normal. Weekly injections of "neptal" ("unephral") were started and continued for three years at home. The parenteral preparation was then replaced by oral "mercloran" (chlormerodrin) tablets, which were given for a further 12 months. She was readmitted to hospital on account of an attack of diarrhoea and vomiting followed by rapidly increasing oedema and oliguria. On admission there was gross anasarca, but the jugular venous pressure was normal. The urine "boiled solid" with protein and contained a few red cells, pus cells, and casts. The serum albumin was low and the serum cholesterol raised. The serum sodium and chloride levels were normal on admission, but fell during the next few days. Despite treatment she died in peripheral circulatory failure 13 days after admission.

Case 3.—A man aged 67 years with syphilitic heart disease. Three years before death he was treated for cardiac failure. When we first saw him, two years before he died, he was again suffering from congestive cardiac failure. His urine contained a trace of protein. The heart failure responded to conventional treatment and the proteinuria disappeared. During the next two years he was kept free of pulmonary oedema by the regular use of mercurial diuretics; neptal and "thiomerin" (mercaptomerin) were given at first, but later mercloran tablets were substituted because his work involved frequent trips abroad, during which he was unable to have injections. Two months before death he attended the out-patient department with oedema of the legs and left forearm; heavy proteinuria was discovered and he was admitted to hospital. The jugular venous pressure at this time was normal and the liver was neither enlarged nor tender. The biochemical findings were as shown in the Table. Despite treatment he failed to improve, and he died suddenly two months after admission.

Case 4.—A woman aged 67 years with degenerative heart disease and auricular fibrillation. This is our only case in which the condition appears to have been reversible. She was first seen five years ago, when she was treated in hospital for congestive cardiac failure. Renal function at that time was normal. Three and a half years later congestive failure recurred; she repeatedly refused to come into hospital and was therefore treated as an out-patient with the usual measures and weekly injections of neptal or thiomerin, and later with mercloran tablets. Moderate proteinuria was discovered, but it was not until eight months after this that she agreed to enter hospital. On admission the jugular venous pressure was raised and the liver was enlarged but not tender. There was pitting oedema to the mid-trunk, and other findings as shown in the Table. She was treated with a low-sodium, high-protein diet, digitalis, and mersalyl. At first a good diuretic response occurred and the jugular venous pressure fell to normal. The proteinuria, however, failed to decrease and the diuretic response diminished (see Chart). Mercurials were stopped, and she improved slowly with symptomatic treatment including high-protein, low-sodium diet. The patient was discharged free from congestive cardiac failure, but with some oedema of the ankles. She has continued to keep well at home, and the serum albumin has risen to 4.2 g. per 100 ml.



Showing response to treatment in Case 4.

Case 5.—A woman aged 61 years who had been treated for congestive cardiac failure for 14 months before her admission to hospital. She had received neptal injections twice weekly for 12 months, and mersalyl three times weekly for two months. On admission there were gross oedema of the limbs and trunk, ascites, and a raised jugular venous pressure, though the liver was not tender. Investigations showed heavy proteinuria (23 g. in the 24 hours),

Table Showing Details of Mercurial Diuretic Therapy and Biochemical Findings

Case No.	Sex and Age	Type of Heart Disease	Mercurial Diuretic and Total Dosage	Urine Protein (g. per litre)	Serum Albumin (g. per 100 ml.)	Serum Cholesterol (mg. per 100 ml.)	Blood Urea (mg. per 100 ml.)	Result
1	F 67	Degenerative	Mersalyl—300 ml. in 3 years	++++	25	800	53–135	Died
2	F 80	Hypertensive	Neptal—294 ml. in 3 years .. .. .. Mercloran—? 1 tablet daily for 12 months	++++ 15	15	470	80–130	Died
3	M 67	Syphilitic	Neptal; thiomerin—176 ml. in 3 years .. Mercloran—660 tablets in 11 months	3–16	29	440–525	28–93	Died
4	F 67	Degenerative	Neptal; thiomerin—60 ml. in 4 years .. Mercloran—112 tablets in 8 weeks	35	25–42	285–280	33–50–35	Improved
5	F 61	? Degenerative	Neptal; mersalyl—260 ml. in 14 months ..	23	18	400	60	

a plasma albumin of 1.8 g. per 100 ml., and plasma cholesterol of 400 mg. per 100 ml. With non-specific treatment the jugular venous pressure fell to normal, and the oedema and ascites diminished but did not clear. The biochemical findings remained virtually unchanged.

Post-mortem Findings

At necropsy the macroscopical and microscopical findings in the kidneys were the same in all three fatal cases. The cortices were swollen and were pale greyish-yellow in colour, contrasting with the dark-grey medullae. There was no evidence of thrombosis of renal veins or inferior vena cava.

Microscopical examination showed the glomeruli to be well preserved and essentially normal. In the renal tubules, however, striking changes had occurred—namely, necrosis and degeneration of the epithelium together with regenerative activity (Special Plate, Fig. 1). Tubular change was focal in distribution and of variable intensity, in some areas amounting to complete necrosis of the epithelium (Special Plate, Fig. 2). Elsewhere there were cloudy swelling and hyaline droplet degeneration; the latter change was often seen, with escape of hyaline droplets from the free margins of epithelial cells into the tubular lumina (Special Plate, Fig. 3). Infiltration of tubular cells with isotropic and anisotropic fat was also present. These necrotic and degenerative changes were most often found in the proximal convoluted tubules, but were also seen in the distal convoluted tubules and in the loops of Henle.

Regeneration of tubular epithelium was a striking feature in all our cases. The large, proliferating cells were irregular and often angular in shape and they had prominent hyperchromatic nuclei (Special Plate, Figs. 4 and 5). Binucleated and multinucleated cells were frequent and occasional mitotic figures were seen. The regenerated cells often did not reconstitute the tubular linings, but instead formed loose masses in the lumina. Hyaline, granular, and occasional cellular casts were seen at all levels of the nephrons; most of them gave positive benzidine reactions of varying intensity. At the sites of some of the casts the tubular epithelium was intact and normal; other casts were associated with necrosis and desquamation of tubular lining cells.

Qualitative tests for mercury were carried out on the kidneys from Cases 2 and 3, and in each gave a strongly positive result. Similarly treated material from a subject who had received mercurial diuretics without suffering any renal damage gave a weakly positive result, and material from a subject never treated with mercurials gave a negative result.

Discussion

There are good reasons for attributing the renal damage in these patients to long-term mercurial diuretic therapy. First, none of them had any previous history of kidney disease, and three of them are known to have had normal urine when treatment with mercurials was begun. Secondly, the pathological changes are similar in each of the three fatal cases, and resemble in quality those seen in acute mercuric chloride poisoning. Thirdly, an excessive amount of mercury was found at necropsy in the renal tubules in two cases. And, finally, no cause other than mercurial damage to the kidneys was found.

The significant pathological finding in these cases was necrosis, degeneration, and regeneration of renal tubules. The glomeruli were normal, which excludes such known causes of the nephrotic syndrome as Ellis's Type II nephritis, renal amyloidosis, and diabetic glomerulosclerosis, and indicates that the tubular changes were primary and not secondary to glomerular damage. The tubular changes recorded here are similar to those reported by previous authors, notably Waife and Pratt (1946) and Preedy and Russell (1953), whose patients, like ours, had no previous renal disease and no glomerular damage. They differ from the characteristic findings in acute mercuric chloride poisoning only in that the tubular damage is less diffuse and that there is no calcification of necrotic and degenerate epithelium.

It seems possible that the nephrotic syndrome is a more frequent complication of long-term mercurial diuretic therapy than the literature would suggest. Increasing oedema and increasing dyspnoea in a cardiac patient may readily be mistaken for a terminal exacerbation of chronic heart failure, and the significance of the massive albuminuria may fail to be appreciated. Two of our patients were sent to hospital with the diagnosis of congestive heart failure, though in neither was the venous pressure raised nor was the liver enlarged or tender.

Since mercurial diuretics are often used for long periods without serious incident, we have tried to determine in retrospect whether there was any unusual factor or combination of factors in our patients which precipitated the tubular damage. We have considered the total dose of mercury, the mercury compound itself, so-called "resistance" to mercurial diuretics, accessory therapeutic measures, and the presence of associated biochemical abnormalities.

(1) *Total Dose of Mercury.*—This was considerable in the three fatal cases (see Table), though many patients have had larger quantities of mercurial diuretics without showing clinical evidence of tubular damage.

(2) *The Mercurial Compound.*—An oral mercury compound, chlormerodrin, was used in three of our cases, and one of the cases recorded in the literature received "mercupurin" ("mercuzanthin"; mercurophylline) by mouth (Derow and Wolff, 1947). It is obvious that oral compounds are more easily administered than parenteral preparations, and this in itself may constitute a danger. It is also possible that oral compounds may be more toxic than parenteral preparations, though on experimental evidence this would seem to be unlikely. Moyer *et al.* (1953) found that in the dog a single large dose of chlormerodrin is completely excreted within 96 hours. According to these workers, only about 10% of ingested chlormerodrin is excreted in the urine, most of the remainder being lost in the faeces. On this assumption, a daily dose of four tablets would represent a weekly absorption of about one-third of the quantity of mercury in 2 ml. of mersalyl.

It seems certain, however, that in man the absorption and excretion of chlormerodrin is very variable. Cáceres and Stauffer (1955) describe a case of mercurialism in a patient who was treated for eleven months with only one tablet of chlormerodrin daily, and, despite this small dose, significant quantities of mercury were still being excreted in the urine two weeks after the drug was discontinued. It is clear that the excretion of these compounds in patients with congestive failure, both with normal and with impaired renal function, requires further investigation.

(3) *Resistance to Mercurial Diuretics.*—Two of our fatal cases (1 and 2) are known to have had little or no response to the mercurial diuretic preceding their terminal admission to hospital. Such absence of diuresis must be regarded as particularly dangerous, since the intratubular concentration of mercury is likely to be increased and the duration of its excretion prolonged.

(4) *Other Therapeutic Measures.*—Restriction of salt and water may, if carried to excess, impair diuresis and predispose to tubular damage by delaying excretion of mercury. In the case described by Preedy and Russell (1953) there was considerable salt depletion, but oliguria occurred only terminally; it is possible, therefore, that salt depletion alone in the absence of oliguria may facilitate renal tubular damage. In one of our cases there was terminal salt depletion, but in this instance the serum electrolytes were normal at the time of admission to hospital, when there was already clinical evidence of tubular damage.

(5) *Hypoproteinaemia.*—It has been suggested by Diengott (1953) that hypoproteinaemia may increase individual susceptibility to the toxic effects of mercurial diuretics, but

we have little evidence on this point. In only one of our cases were the serum proteins estimated before the onset of the nephrotic syndrome, and in this instance they were normal; the estimation was, however, carried out four years before the appearance of the nephrotic syndrome.

In the prophylaxis of this condition close supervision of patients treated with mercurial diuretics, including regular examination of the urine, is essential. It is noteworthy that two of our three fatal cases had no hospital supervision in the three years preceding death, and the third patient travelled round the Continent for long periods with a supply of mercloran tablets.

The principal warning signs of the onset of the nephrotic syndrome complicating mercurial diuretic therapy are: (1) Failure of albuminuria to decrease after a satisfactory diuresis. This, we think, is by far the most valuable indication of tubular damage. Case 4 undoubtedly had congestive cardiac failure, and this alone might have been responsible for the proteinuria. Mersalyl produced a satisfactory diuresis, but in spite of this the heavy proteinuria persisted (see Chart), indicating serious tubular damage. (2) Increasing oedema, especially of the arms and face, in the absence of other signs of cardiac failure. (3) Absence of diuresis after mercurial therapy. This has been ascribed to tubular damage, but in our experience it is a late and unreliable sign.

Treatment of the fully developed syndrome is unsatisfactory. BAL (dimercaprol), corticotrophin, ion-exchange resins, and decapsulation of the kidneys have all been tried without benefit.

The survival of one of our patients who received no specific therapy indicates that in some circumstances the condition is reversible. Early recognition of the condition and cessation of mercurial therapy before irreparable renal damage has occurred offer the best chance of recovery.

Summary

The nephrotic syndrome complicating congestive heart failure is reported in five patients who received mercurial diuretics for long periods.

The clinical features, and the pathological findings in three fatal cases, suggest that the renal lesion was due to mercury. Possible contributory factors are considered.

Early recognition of the condition is of the utmost importance if a fatal outcome is to be avoided.

The most useful evidence of tubular damage is persistence of albuminuria despite a satisfactory diuresis in response to mercurial therapy.

Our thanks are due to Dr. Una Ledingham and Dr. Wallace Brigden for permission to publish Cases 1 and 5 respectively.

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Middlesex had its record lowest infant mortality rate in 1957. There were 561 deaths of infants under 1 year old, giving a rate of 17.7 per thousand live births. This is 5.3 below the rate for England and Wales as a whole. As elsewhere, deaths from lung cancer increased, being 1,166, or 76 more than in 1956. Despite an excess of live births over deaths amounting to more than 9,000, the population of the county again fell owing to removal from it. At about 2¼m. the population was 2,000 lower than in 1956.

NEPHROSIS DUE TO MERCURIAL DIURETICS

BY

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Following the work of Saxl and Heilig in 1920 on the diuretic effect of organic compounds of mercury, mercurial diuretics have been used extensively to control oedema in cardiac failure and less extensively to control oedema secondary to renal disease. At first these drugs were used with considerable caution, for it was well known that inorganic mercuric salts were apt to cause renal damage. However, these fears were soon overcome, since cases of renal damage due to mercurial diuretics have been infrequent. The first case was reported by Sprunt in 1930, although others have since come to light (Tarr and Jacobson, 1932; Rosenthal, 1933; Waife and Pratt, 1946; Bruno, 1948; Preedy and Russell, 1953). The use of mercurial diuretics is now so widespread that perhaps the danger is being overlooked. The purpose of this report is to record a case in which a mercurial diuretic is thought to have produced the renal damage, and to show by microdissection the site of the lesions, which is similar to that described for inorganic mercury.

Clinical Course

A woman of 69 was admitted to hospital on April 18, 1957, with a four-months history of progressive heart failure together with angina of effort for two months. Her health prior to this was excellent. On examination she was found to have a trace of ankle oedema. Her pulse was 85 and regular, and B.P. 140/90. The apex beat was in the fifth intercostal space 3¼ in. (9 cm.) from the midline; a harsh systolic murmur was audible to the left of the sternum, maximal in the fourth interspace, and a systolic thrill was palpable in this area. Crepitations were heard at both lung bases and the liver was palpable. The urine contained no albumin.

A diagnosis of ischaemic heart disease was made and the patient was given weekly injections of 2 ml. of mersalyl. The response was satisfactory and the patient was discharged home after three weeks. The urine was protein-free on discharge.

Weekly injections of 2 ml. of mersalyl were continued at home and her condition remained satisfactory for two months. Oedema then reappeared and she was readmitted on September 15. On examination on admission there was gross oedema of the legs, of the trunk to the level of the mid-dorsal region, and of the forearms and hands. The pulse rate was 96 and regular, the B.P. 140/80. The jugular venous pressure was raised 1 in. (2.5 cm.). The systolic murmur was unchanged. There were small effusions at each base and moist adventitia in the lungs. The urine was found to contain a considerable quantity of protein, and later determinations revealed a daily urinary excretion of 11.5 to 35 g. Plasma proteins on admission were as follows: total 5.3 g./100 ml. (albumin 1.5 g., globulin 2.96 g., fibrinogen, 0.84 g.). The blood urea was 46 mg./100 ml.; sodium, 134 mEq/l.; potassium, 4.7 mEq/l.; chloride, 91 mEq/l.; CO_2 combining power, 26 mEq/l.; bilirubin, 0.2 mg./100 ml.

Because of these findings the mersalyl was stopped and acetazolamide substituted. Neither this nor intravenous dextran produced a diuresis, and the patient died on September 27.

Necropsy Report

At necropsy the gross oedema noted on admission was unchanged. The heart was found to be slightly enlarged owing to left ventricular hypertrophy, and just above the midpoint of the interventricular septum there was a defect 2 mm. in diameter. The heart valves were normal. There was extensive atherosclerosis of the coronary arteries with patchy calcification, and the aorta and major arteries throughout the body were atherosclerotic. Each pleural cavity contained half a pint (284 ml.) of clear straw-coloured fluid, and the lungs were congested and oedematous. The liver and spleen showed the changes of chronic passive congestion.

The kidneys were of normal size (left 160 g., right 170 g.) and there was persistence of foetal lobulation. The capsules stripped easily and the subcapsular surface was smooth. The parenchyma was congested and the corticomedullary junction was indistinct.

FIG. 1.—Tangential section of proximal tubule, showing extensive epithelial intracellular deposits of fatty material. (Fettrot. ×360.)

Histological examination of the tissues confirmed the presence of widespread vascular congestion, but the chief interest lay in the kidneys. Sections from the kidneys were stained with H. and E., with P.A.S., and by von Kossa's method. Gelatin-embedded tissue was stained for fat by the method of Fettrot. The glomeruli were substantially normal apart from the presence of eosinophilic granular material in Bowman's space, though occasional glomeruli were shrunken. The capillaries were bloodless and there was no thickening of the basement membrane or proliferation of epithelium. Tubular damage was prominent, with flattening and desquamation of the epithelium in the proximal and distal convoluted tubules. The lumen of the tubules which were dilated was filled with eosinophilic granular debris and necrotic cells. The remaining damaged cells lining the convoluted tubules had a foamy and vacuolated cytoplasm. The nuclei were often pyknotic. Though some of this appearance may be due to post-mortem autolysis, there was an undoubted increase in the intracellular fat (Fig. 1). Regenerating epithelium was not seen in any of the material studied. Nowhere was there evidence of calcification of either the tubular epithelium or the debris in the lumen. There was marked oedema of the interstitial tissue, with scattered chronic inflammatory cell-infiltration. Apart from the congestion the vasculature was normal.

Microdissection of the nephrons was carried out by the method previously described by Darmady and Stranack (1957). The total number of nephrons appeared to be within normal limits. The glomeruli showed no anatomical abnormality. (By this technique it is not possible to identify with accuracy glomerular abnormalities.) The proximal tubules, although normal in outline, showed localized and, in places, extensive deposits of fat-containing material, giving a strongly positive result with Nile blue (Fig. 2A). The position of these lesions corresponded in general with those described by Oliver, MacDowell, and Tracy (1951) for mercuric chloride. In other areas the arrangement of the epithelium was normal; the loop of Henle showed no damage. In the distal tubules, however, there were extensive and focal areas of epithelial fat replacement, with distortion of the epithelium arrangement (Fig. 2B). The atrophy seen might have been accounted for by the age of the patient.

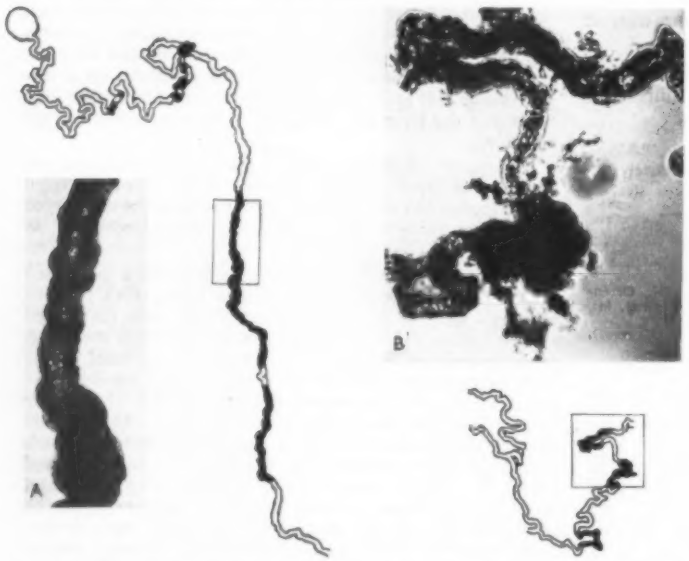

FIG. 2.—Semi-diagrammatic line drawing of proximal tubule and distal tubule to indicate areas of fat replacement, seen in black. A, Portion of proximal tubule showing focal areas of fat replacement. (Phase contrast. ×100.) B, Portion of distal tubule showing focal areas of fat replacement. (Phase contrast. ×100.)

Comment

The appearances here described are in agreement with the gross and microscopical findings in cases of renal damage due to inorganic and organic mercurials. Damage in the convoluted tubules is the salient feature, and it is most probable that damage in this section of the nephron is a function of the absorptive activity of the convoluted tubules raising the local concentration of mercury. The localized areas of cell necrosis and fatty degeneration suggest that this was due to the direct effects of mercury, which is a powerful protoplasmic poison. In the case described fatty degeneration of the renal epithelium was a prominent feature. This finding has been reported in only two cases (Waife and Pratt, 1946; Preedy and Russell 1953). However, in the cases described earlier in this issue (p. 1274) microdissection in two of the cases also showed fatty epithelial degenerative change mostly confined to the proximal tubules, but also to a lesser extent in the distal tubules. Calcification of the damaged cells and luminal debris, though absent in this case, has been a prominent feature in some cases of poisoning with inorganic mercury (Tarr and Jacobson, 1932; Allen, 1947; Bruno, 1948). In cases reported by these authors the deposits of

"calcium" appeared within a few days of the administration of mercury. This is in marked contrast with our experience in producing experimental nephrocalcinosis, which was usually found to take 10 to 14 days. Since von Kossa's stain for calcium is not specific it is possible that at least some of the stainable "calcium" reported by these authors was in fact a phosphate mercury complex.

Specific glomerular changes other than the accumulation of eosinophilic material in Bowman's space have not been described following the administration of mercurial diuretics. However, shrunken glomeruli of the type described earlier were found in the kidneys of rabbits which had received mercuric chloride (Edwards, 1942). These shrunken glomeruli may be of considerable importance in this case, since it is recognized that in the nephrotic syndrome there is not only tubular dysfunction with some resultant failure to reabsorb protein, but also increased permeability of the capillary tufts in the glomerulus (Hardwicke and Squire, 1955). The nephrotic syndrome has not been a feature of previously recorded cases of fatal renal damage following mercurial diuretics, and this might be explained by the fact that the glomerular lesion is not a constant feature in these cases.

From the clinical angle mercurial diuretics are now widely used. The possible action of this drug as a nephrotoxin does not seem to be as fully recognized as it should. In this case the renal tubular damage had apparently become irreversible before steps to institute an alternative diuretic could be arranged. It is not easy to suggest methods for the recognition of the onset of renal failure. The one sign which may be of value is the onset of increasing proteinuria.

Summary

A case of the nephrotic syndrome following the administration of a mercurial diuretic is described.

The salient histological feature was necrosis and fatty degeneration without calcification of the epithelium in the convoluted tubules. In addition a number of the glomeruli were shrunken.

The significance of the dual lesion in the production of the nephrotic syndrome is discussed.

The observation of increasing proteinuria in patients under treatment with mercurial diuretics suggests that renal damage may be occurring, and that prompt steps should be taken to institute alternative diuretics.

Our thanks are due to the Medical Research Council for an expenses grant. We are grateful to Dr. J. C. Prestwich, under whose care the patient was for her final illness, for his permission to publish this case. We are also grateful to Mrs. S. J. W. East for the line drawing and to Mr. A. E. Clarke, F.I.M.L.T., for the photomicrograph.

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The Medical Research Council's medical mycology committee has recently revised *Nomenclature of Fungi Pathogenic to Man and Animals* (M.R.C. Memorandum No. 23, H.M.S.O., price 1s. 3d. net.). The memorandum lists the names for fungi and for fungal diseases which the committee recommends should be used in Britain; it also includes notes on why some of the names are preferred and a list of rejected names.

LARYNGEAL STRIDOR IN RHEUMATOID ARTHRITIS

BY

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[WITH SPECIAL PLATE]

Arthritis of the cricoarytenoid joint is one of the more unusual manifestations of rheumatoid arthritis and has been accepted by most observers as the cause of laryngeal stridor which sometimes occurs late in the disease. We have recently encountered five patients with unmistakable evidence of advanced rheumatoid arthritis who presented with stridor. The onset of this complication occurred when the generalized joint disease appeared to be quiescent, and tracheotomy became necessary in four cases. Clinical examination in three of the cases indicated a bilateral abductor paralysis of the vocal cords. As the difficulty of differentiating between an arthritis of the cricoarytenoid joint and a bilateral abductor paralysis with disuse fixation is well recognized, the death of two of our patients provided material for a detailed microscopical study of this problem.

Case 1

The patient worked in a rolling mill until the age of 57, when he developed rheumatoid arthritis. He received a variety of physical treatments at a local spa, but these did not include gold or other injections. Gradually the disability increased so that he had to find lighter work. In December, 1953, at the age of 62, and two years before his death, he developed a respiratory infection with hoarseness. At no time in the past had there been any laryngeal symptoms, and there was no local pain or dysphagia on this occasion. Three weeks later his breathing became very distressed owing to respiratory obstruction. Both vocal cords were touching, and an emergency tracheotomy was performed. After recovery from the operation the nature of the laryngeal lesion was more fully investigated. Indirect laryngoscopy showed a symmetrical appearance with a vocal gap of 2–3 mm. posteriorly. No movement occurred on inspiration or expiration, but the cords met on phonation. On straining, the larynx as a whole contracted. Direct laryngoscopy was performed under thiopentone and succinylcholine chloride anaesthesia, and the mobility of the arytenoids tested by grasping them in a pair of Paterson's forceps. Movement of the cricoarytenoid joint was found to be unrestricted. Because of these findings the lesion was regarded as a bilateral abductor paralysis rather than a cricoarytenoid arthritis. Neurological examination showed no cause for a paralysis of the vocal cords, so the case was finally diagnosed as idiopathic bilateral abductor paralysis of the larynx.

The patient managed to get about at home fairly well for the next 18 months until his dyspnoea returned, eventually being present even at rest. When examined at this time he showed undoubted changes of advanced burnt-out rheumatoid arthritis, with permanent deformities in the hands. In addi-

tion there were marked finger-clubbing and the characteristic features of a diffuse interstitial fibrosis of the lungs, with tachypnoea at rest, hyperventilation, central cyanosis, and persistent loud rales over both lungs. His general condition was fair and there was no evidence of vitamin deficiency, peripheral neuritis, or other neurological disorder, nor of generalized arteriosclerosis. There was no disease of the skin. The temporo-mandibular joints were normal.

A radiograph of the chest showed a diffuse interstitial fibrosis which had advanced since an earlier radiograph taken a few days after the tracheotomy. Barium swallow was normal. The Wassermann and Kahn reactions were negative. A blood examination showed a moderate anaemia. The plasma proteins were normal. An electrocardiogram suggested right ventricular hypertrophy.

Treatment in hospital included antibiotics to control the mild respiratory infection and oxygen to relieve the cyanosis and dyspnoea. These measures proved of no avail, and he died rather suddenly four weeks later from bronchopneumonia.

Post-mortem Examination

The immediate cause of death was a recent myocardial infarction of the anterior wall of the left ventricle due to a thrombus in the left descending coronary artery. The heart weighed 360 g. and the right ventricle was hypertrophied. The pericardium was adherent. There was obliteration of both pleural sacs from old adhesions. The lungs were small and indurated as the result of an advanced interstitial fibrosis with some superficial cystic changes. The lower lobes revealed a patchy bronchopneumonia. There was no evidence of an old mediastinitis or of fibrosis around the larynx. The other internal organs were normal. The cricoarytenoid joints were fully mobile. The brain and spinal cord were removed and the vagus with its laryngeal branches was dissected out. These nerves appeared much thinner than normal. Sections were taken from representative levels throughout the central nervous system and from these nerves.

Microscopical examination showed a thickened, chronically inflamed synovial lining of the cricoarytenoid (Special Plates, Figs. 1 and 2) and cricothyroid joints and a thick-walled, chronically inflamed subhyoid bursa. Several foci of chronic inflammatory cells were present in the subcutaneous tissues of the neck. The laryngeal muscles showed a neural atrophy. The superior and recurrent laryngeal nerves showed severe demyelination and degeneration of the axis cylinder, and this was present but less marked in the vagus (Special Plate, Fig. 3). No obvious cause for the neuropathy could be seen in the sections examined. The nerve cells of the nucleus ambiguus and other cranial-nerve nuclei appeared intact and there was no evidence of motor neurone disease. The brain showed marginal gliosis and scattered small focal areas of old infarction consistent with arteriosclerotic brain atrophy.

Case 2

A woman of 65 years was first seen by us in 1955 during an attack of bronchitis. She stated that she had rheumatic fever when she was 30 years of age, and for more than 20 years had suffered from rheumatoid arthritis with progressive disability. When she was 54 hoarseness and stridor developed, without any associated pain or dysphagia. Indirect laryngoscopy showed appearances which were considered to be due to bilateral abductor-nerve palsy. A tracheotomy was done to relieve the respiratory obstruction, and she has worn a rubber tube ever since. Following the operation she has been subject to recurrent attacks of asthmatic bronchitis. She had never received gold injections.

Clinical examination in November, 1955, showed good general nutrition and unmistakable signs of severe rheumatoid arthritis with gross deformity. There was no cyanosis or clubbing of the fingers, but persistent rales were audible over the left lower lobe with occasional scattered rhonchi. The blood pressure was 190/120 mm. Hg. All superficial pulses were present, although there was some generalized arteriosclerosis. There were no lesions of the skin. The voice was weak and croaking, and accomplished by closure of the tracheotomy opening with the finger. Indirect laryngoscopy showed hypertrophy of the false cords and a symmetrical appearance. The vocal chink was 1–2 mm., with no movement occurring on respiration, but slight adduction on attempted phonation. The larynx as a whole contracted on straining. Under thiopentone and succinylcholine chloride anaesthesia some reduction in the normal mobility of the arytenoids was found. Radiographs of the skeleton showed general osteoporosis with mild subluxation of the cervical vertebrae and advanced rheumatoid changes in the small joints of the hands. A chest radiograph revealed partial collapse of the left lower lobe. An electrocardiogram showed inversion of T waves. There was a mild anaemia with an eosinophilia of 14%. The Wassermann and Kahn reactions were negative and the plasma proteins normal.

During the last 18 months her condition has changed little, and it is considered that the laryngeal findings could equally well be those of a cricoarytenoid arthritis or of a bilateral abductor paralysis with disuse fixation.

Case 3

A married woman aged 61 was first seen by us in 1955 on account of severe respiratory obstruction due to laryngeal stridor. She had suffered from severe rheumatoid arthritis for the previous 30 years. At the age of 40 an ulcer developed on the inner side of the lower third of the right leg, which broke down repeatedly over the next 20 years. Ulceration developed between the first and second toes of the right foot, and this ultimately became gangrenous. The feet were otherwise warm, while the arterial pulses were normal. Investigations at the age of 54 showed a severe iron-deficiency anaemia, a histamine-fast achlorhydria, and granulocytopenia with hypoplasia of the granulocyte series of the bone marrow. A year later difficulty in breathing was noted, and laryngeal examination by Mr. J. H. Cobb showed a bilateral abductor-nerve palsy. Tracheotomy was not considered necessary, for her activities were severely limited by her arthritis. On her final admission she was frail, wasted, and crippled with chronic rheumatoid arthritis. The stridor, which had been caused by a mild respiratory infection a week previously, rapidly became worse, and an emergency tracheotomy was performed under general anaesthesia, preliminary intubation having been accomplished under local analgesia. The vocal cords were closely approximated, and remained so when the patient was breathing freely through the tracheotomy tube and also when this was momentarily closed. The arytenoids appeared to be freely mobile. The patient died 16 hours later.

Post-mortem Examination

Death was due to a patchy bronchopneumonia in both lungs, with a small recent infarct in the right upper lobe. The heart weighed only 200 g. The coronary arteries were patent and there was only minimal atheroma of the aorta. The other internal organs were free from gross disease. Examination of the larynx showed no evidence of fixation or of limitation of movement of the cricoarytenoid joints. The brain, spinal cord, vagus, and superior and recurrent laryngeal nerves were removed for microscopical examination. The nerves appeared much thinner than normal. The cricoarytenoid joint was free from any arthritic process. The laryngeal muscles showed a severe neural atrophy (Special Plate, Fig. 4). The vagi, superior laryngeal, and recurrent laryngeal nerves showed demyelination with varicose, swollen axis cylinders. These changes were associated with severe reduction of the lumen of the vasa nervorum due to intimal proliferation (Special Plate, Fig. 5). The inferior laryngeal branch of the inferior thyroid artery, which accompanies and supplies the recurrent laryngeal nerve, showed thombosis with recanalization by two minute channels. The internal elastic lamina was fragmented, and

calcification had occurred in this and in the proliferated intima (Special Plate, Figs. 6 and 7). The nerve cells of the nucleus ambiguus and other cranial-nerve nuclei appeared intact, and there was no evidence of motor neurone disease.

Case 4

The patient, a man aged 65, used to work as a springer in a steelworks. Rheumatoid arthritis developed at the age of 34, and within three years he was severely disabled. Aspirin and frequent courses of physiotherapy did not halt the disease, although gradually the pain in the joints became less. He did not receive gold injections. During the three years preceding his examination by us in 1956 his voice had become husky at times, although there was no local pain or dysphagia, and his breathing was not embarrassed until a few weeks previously, when he had begun to have alarming choking attacks at night.

Examination in hospital in May, 1956, showed the general features of severe chronic rheumatoid arthritis. There was mild respiratory stridor, but no cyanosis or clubbing. Moderate general arteriosclerosis was present, affecting particularly the arteries of the upper limbs. Indirect laryngoscopy showed a symmetrical appearance with a vocal gap of 2–3 mm. There was no movement on respiration, but the cords met on phonation and the larynx as a whole contracted on straining. Examination under thiopentone and succinylcholine chloride anaesthesia showed that the mobility of the arytenoids was limited. There was roughening of the cords at the anterior commissure which was suspected to be neoplastic. This appearance became more clearly that of a carcinoma, and on August 27, 1956, a biopsy and tracheotomy were performed. The microscopical appearances of the biopsy tissue were those of a squamous-cell carcinoma which has responded completely to radiotherapy. He remains fairly well, but still wears a tracheotomy tube.

Case 5

The patient, a married woman of 67 years, had suffered from rheumatoid arthritis for 31 years. For about a year she had been subject to mild attacks of asthmatic bronchitis. She was referred to us by Dr. H. F. West, of the Rheumatism Research Unit, Sheffield, because of an inspiratory stridor and maxillary sinusitis. There had been no local pain in the jaws or larynx and no dysphagia. Laryngeal examination showed a symmetrical appearance. The vocal gap was 3 mm., and did not vary with respiration, but could be closed on phonation. Under general anaesthesia the arytenoid cartilages were completely lax. Antral lavage was carried out.

The degree of stridor and respiratory embarrassment is at the moment mild, and tracheotomy is not required.

Discussion

Although it is well recognized that in any polyarthritic condition the process may affect the cricoarytenoid joint (Ellis, 1951 ; De Vido and Ancetti, 1952), until recently there have been scant references in the literature. The appearance in the last few years of several reports of laryngeal involvement in rheumatoid arthritis indicates renewed interest in the subject and suggests that the condition is not such a rarity. It will be seen from the Table that these cases have a similar pattern, with the onset of respiratory obstruction in the sixth or seventh decades, following after the onset of rheumatoid arthritis by many years, when the joint condition was either quiescent or only mildly active. The period of increasing respiratory obstruction varied from a few months to two years. The four cases reported by Montgomery *et al.* (1955) showed a similar age incidence for both the rheumatoid arthritis and the laryngeal symptoms. These workers discussed the difficulties of the differential diagnosis of immobility of the vocal cord. They attached most importance to the history, painful spatula test, and inspiratory bowing of the cords in making a diagnosis of arthritis rather than of laryngeal palsy, but even these can be inconclusive. Only the ultimate demonstration of typical rheumatoid changes in the joints or the finding of degeneration in the recurrent laryngeal nerves makes the diagnosis certain.

Table Showing Age of Onset of Rheumatoid Arthritis and of Respiratory Obstruction

Case No.	Age of Onset	
	Of Rheumatoid Arthritis	Of Respiratory Obstruction
1	57	62
2	30	54
3	31	55
4	34	63
5	36	66

Similar difficulty in the differential diagnosis was encountered by Saunders (1956) and Copeman (1957). The latter reported three cases of rheumatoid arthritis developing recurrent attacks of hoarseness late in the course of the illness. As recurrent paralysis of peripheral nerves in association with exacerbations of rheumatoid arthritis has not been recorded, it was considered more probable that arthritis of the cricoarytenoid joints was the explanation. Tracheotomy was not necessary and no histological confirmation was possible. The most convincing case is that of Pearson (1957), in which post-mortem histological examination showed villous proliferation of the synovial membrane of the cricoarytenoid joint. No mention was made of the laryngeal muscles and nerves.

Baker and Bywaters (1957) recorded an unusual case of laryngeal stridor which was considered to be due to rheumatoid involvement of the cricoarytenoid joint. There were several features in this case suggestive of systemic lupus erythematosus, in which peripheral-nerve palsy sometimes occurs on a vascular basis (Heptinstall and Sowry, 1952). Despite vascular lesions elsewhere causing nail-fold thrombosis, a local arthritis in the laryngeal joint was favoured as a diagnosis even though the laryngeal picture resembled that of a bilateral abductor paralysis. No microscopical confirmation was possible, and tracheotomy was avoided by the use of delta-cortisone. Even this therapeutic response to cortisone cannot be relied upon as a confirmation of the diagnosis of rheumatoid arthritis of the cricoarytenoid joints, as in one of the cases of Montgomery *et al.* the laryngeal condition developed during cortisone treatment, and in another case the symptoms became worse.

Hart and Mackenzie (1955) described the case of a man of 45 with a 15-year history of rheumatoid arthritis who had an attack of dyspnoea followed by stridor necessitating tracheotomy. The cause of the stridor was thought to be abductor palsy, although this could not be explained except possibly on the basis of deep *x*-ray therapy for thyrotoxicosis. He died four years later, and at necropsy there was microscopical evidence of fibrosis in the region of the vocal cords. Unfortunately, no reference to the state of the cricoarytenoid joints or of the recurrent laryngeal nerves was made.

Thus, apart from the case described by Pearson (1957) in which the cricoarytenoid joint was sectioned and the arthritis confirmed, the diagnosis in the other cases is accepted as the most likely on clinical grounds, although the difficulty in differential diagnosis is acknowledged. In none of the cases reported were the laryngeal nerves and muscles studied. The death of two of the patients in our series of five enabled a complete examination of the laryngeal joints, muscles, and nerves to be made together with a neuropathological study of the central connexions with the brainstem and the descending pathways from the cortex.

In Case 1 the cricoarytenoid joint was still freely mobile, although its synovial sheath was thickened and showed chronic inflammation. The cricothyroid joint and the subhyoid bursa showed similar chronic inflammation. The inflammatory reaction was non-specific and not typically rheumatoid, although this may have been responsible. As there were scattered foci of chronic inflammatory cells in the subcutaneous tissue of the neck there was evidence of additional chronic infection from the tracheotomy. The

laryngeal muscles showed neural atrophy and there were severe degenerative changes in the superior and recurrent laryngeal nerves and vagus. No indication as to the cause of this neuropathy was seen in the numerous sections examined. Such causes of nerve degeneration as vitamin deficiency, virus disease (Critchley, 1946), toxic effects from heavy metals, and amyloid (Missen and Taylor, 1956) were excluded. Thyroid disease was absent, and no tumour or disease process could be found in the mediastinum, thoracic inlet, neck, or nasopharynx. The brain-stem was normal, but the cerebrum showed several small scattered infarcts of varying age due to arteriosclerosis. As death had resulted from coronary thrombosis the possibility of ischaemic neuropathy was considered, but no evidence to support this could be found.

It is claimed that rheumatoid arthritis can produce both a polymyositis and neural atrophy due to pressure palsy on nerves by the diseased joint (Adams *et al.*, 1953). No evidence of polymyositis was found in the laryngeal muscles, while the vagus and its branches are sufficiently distant from joints likely to be affected by rheumatoid arthritis that a pressure palsy is not possible. No focal lesions in the nerves or muscles as described in rheumatoid arthritis by Freund *et al.* (1942), Steiner *et al.* (1946), and Cruickshank (1952) were found. The cause of the neuropathy in this case remains obscure (Ellis, 1946; Huppler *et al.*, 1956).

In Case 3 the cricoarytenoid joints were healthy, but the muscles again showed neural atrophy which had resulted from ischaemic neuropathy. Gross obliterative endarteritis of the vasa nervorum was found. A variety of vascular changes have been described in rheumatoid arthritis (Sokoloff *et al.*, 1951; Cruickshank, 1954; Ball, 1954; Bywaters, 1957). These ranged from intimal proliferation to a severe necrotic arteritis resembling polyarteritis nodosa. Vessels in the heart, muscles, and nerve sheaths were most frequently involved. The changes in the vasa nervorum could be of rheumatoid origin, while the severe calcification might have resulted from metastatic calcification in necrotic tissue from the bones of limbs kept fairly immobile by the joint disease or possibly as a superimposed arteriosclerotic effect. The leg ulceration and gangrene of the toes were regarded as further indication of generalized vascular disease of rheumatoid origin (Bywaters, 1957; Allison and Bettley, 1957). Systemic lupus erythematosus was considered as a possible diagnosis, but could not be substantiated.

Thus, although in cases of rheumatoid arthritis in which stridor develops involvement of the cricoarytenoid joint may be responsible, it is not the only factor, and nerve degeneration can be the cause. That this may be of ischaemic origin related to a "rheumatoid" arteritis of the vasa nervorum fits in with the wider concept of "rheumatoid disease" (Ellman and Ball, 1948; Cruickshank, 1957) as both a pathological and clinical entity, rather than "rheumatoid arthritis," in cases presenting unusual or more diffuse features.

Summary

The difficulty of distinguishing between an arthritis of the cricoarytenoid joints leading to stridor and a bilateral abductor paralysis of the vocal cords is emphasized. Clinical examination may not provide sufficient evidence, and in the final analysis microscopical examination of the joints, muscles, and nerves is needed.

Five patients suffering from advanced rheumatoid arthritis are described, each of whom developed laryngeal stridor, and in four instances tracheotomy became necessary. Two of the patients died, and post-mortem examination revealed indisputable evidence of nerve degeneration and mobile cricoarytenoid joints, even though chronic inflammation of the joints was present in one case. In the second case the microscopical changes in the nerves appeared to be due to ischaemic neuritis resulting from a rheumatoid type of arteritis of the vasa nervorum.

Although rheumatoid changes in the cricoarytenoid joints do occur, it is suggested that in some cases the stridor is due to abductor paralysis resulting from nerve degeneration.

We wish to thank Dr. H. F. West, who referred Case 5, for his helpful advice; Mr. J. H. Cobb for his interest and for allowing us access to his records on Case 3; Dr. A. J. N. Warrack for carrying out the two post-mortem examinations; and Professor D. H. Collins for his valued opinion and useful criticism.

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CERVICAL MYELOPATHY PRESENTING AS PERIPHERAL NEUROPATHY

BY

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[WITH SPECIAL PLATE]

Considerable attention has recently been given to cervical spondylosis and its neurological complications (Brain *et al.*, 1952; Clarke and Robinson, 1956; Bradshaw, 1957). The term "spondylosis" refers to the chronic degenerative changes in the cervical spine occasioned by disk degeneration, which is usually the result of senile changes, but which may appear in the presence of congenital bony anomalies or as a delayed sequel to injury. The acute cervical prolapsed intervertebral disk does not come within the scope of the term, and it must be rigorously excluded from considerations of this subject, especially therapeutic. "Cervical myelopathy" has been used to describe those cases in which the neurological complication of spondylosis is manifested principally by a spinal-cord lesion, but some degree of coexisting root involvement can rarely be entirely excluded.

It is well known that the clinical results of nervous-tissue compression by cervical spondylosis are varied, both in their presenting features and in the eventual clinical picture. Thus it is possible to observe syndromes which may closely simulate known diseases of the nervous system. The commonest of these are disseminated sclerosis, cervical-cord neoplasm, motor neurone disease, and syringomyelia; but differentiation on clinical grounds alone is often possible. The possibility of coincidental cervical spondylosis with a neurological

disease other than cervical myelopathy is, however, also an important consideration (*Lancet*, 1955; Bradshaw, 1957).

Cases of cervical myelopathy resembling peripheral neuropathy do not appear to be common, and the present paper describes two of them. Furthermore, they demonstrate a pathological feature which may be of aetiological importance in some cases.

Case 1

A 62-year-old labourer was first seen as an out-patient on April 19, 1955. He worked in a soap factory, and for many years carrying sacks on his shoulders had been part of his job. For two weeks he had noticed a severe tingling of all his fingers and toes and the soles of his feet, which seemed to be aggravated by carrying heavy loads. For a similar length of time there had been paraesthesiae and tightness round his waist.

On examination, neck movements were found to be restricted and there were chronic degenerative changes of the finger-joints. The nervous system was normal except for some blunting to pinprick distally in the limbs, and slight impairment of vibration sense at the ankles, which may have been in keeping with his age. Radiographs of the cervical spine showed a severe degree of spondylosis, maximal at C4–5, but it was thought to be consistent with the patient's age and occupational habits.

The initial clinical impression was that of a peripheral neuropathy, but various inquiries and investigations did not reveal an aetiology. He was treated conservatively, but continued to complain of acroparaesthesiae and soon found that he was unable to hold small objects in his hands. While being observed in the out-patients' department he was found to have an increasing defect of vibration appreciation in the legs. Next extensor plantar responses, first on the left side and then bilaterally, became evident, and finally an inverted left supinator jerk appeared. His only additional symptom was severe pain in the neck produced by neck flexion.

He was now admitted to hospital, and his cerebrospinal-fluid contents were shown to be normal; however, when the neck was fully extended and the jugular veins were compressed there was a manometric block which could not be demonstrated with the neck in other positions. Myelography demonstrated a complete block at the C4–5 disk space (Special Plate, Fig. 1) with the neck in full extension; indentations of the radio-opaque material were both anterior and posterior. Smaller degrees of anterior indentation were present at other cervical levels, and throughout the spinal canal there was evidence of mild intervertebral protrusions.

As his symptoms were relatively mild, and as he had already begun to improve subjectively with physiotherapy alone, active treatment was not recommended. Since discharge from hospital 1½ years ago he has returned to work, but now has a light job and does not carry loads. He has been followed carefully as an out-patient, and despite the absence of specific treatment he continues to report definite improvement; there has, however, been little change in the abnormal neurological signs.

Comment.—There can be no doubt that the whole clinical picture in this case was due to the cervical-spine lesion, and it has been possible to observe it from an early stage of its existence. The truncal sensation is compatible with a cervical-cord lesion and has been described in this condition (Clarke and Robinson, 1956), but thoracic cord or root involvement by spondylosis, of which there was some myelographic evidence, could not be excluded.

Case 2

A mechanical engineer aged 67, who had indulged in heavy labouring work, attended the out-patients' department on March 6, 1956, complaining of tingling and weakness of the fingers for six months. Furthermore, he had a peculiar sensation in the hands "as though they were covered with oil," and he found that he was unable to manipulate small objects such as buttons. For four months he had noticed a mild weakness of the legs. On examination, limitation of neck movements and slight weakness of the hands were found. The reflexes were all present and symmetrical and the plantar responses flexor. Distally, in the arms more than the legs, there was diminution of vibration and joint sense. Radiographs of the cervical spine showed a severe degree of spondylosis, but not more than might be expected for his age. It was thought that he had a type of peripheral neuropathy, but, as in Case 1, a search for an aetiological agent was fruitless and again he was treated conservatively and observed carefully.

While attending as an out-patient, however, signs of pyramidal-tract involvement became evident. His symptoms had not changed, and were limited to the hands and legs. Attention was now directed toward the cervical spinal cord and he was admitted to hospital. The cerebrospinal-fluid contents were normal, but a manometric block only with the neck in extension was found. Myelography proved that there was an almost complete block at the level of the C3–4 intervertebral disk space when the neck was fully extended. Again there was a posterior as well as an anterior component to the filling defect (Special Plate, Fig. 2) and the column of radio-opaque substance was deformed at other intervertebral levels.

The problem in this patient was very similar to that in Case 1, and he was also given physiotherapy to the legs as well as other non-specific measures. He has now been observed carefully for 1½ years, and, although showing little or no objective change, he reports continuing improvement and finds that his symptoms give him little trouble.

Comment.—Once more, despite the initial appearances, these and the subsequent developments can all be accounted for by the cervical-cord lesion due, as in Case 1, to both anterior and posterior compression at a single level. As in Case 1, the myelographic findings confirmed the manometric observations.

Discussion

At the onset of their illness each patient had a combination of symptoms and signs which suggested a diagnosis of peripheral neuropathy. They had peripheral paraesthesiae or dysaesthesiae, and the clinical findings were in keeping with this conclusion. A search for an aetiological agent was in each case unsuccessful, and while under observation there was an increase of the sensory deficit and they showed evidence of pyramidal-tract involvement, attention being directed to the cervical region. They had both done heavy manual work, and each had limited neck movements with radiological evidence of severe cervical spondylosis; but, although a cervical-cord-compressing lesion had been considered initially, it was not thought to be likely. Subsequent events and the cerebrospinal-fluid and myelographic findings showed this opinion to be incorrect.

Craig and Shelden (1940) have pointed out the bizarre clinical results of a cervical-cord-compressing lesion, and it is possible to find cutaneous sensory alteration of a "glove and stocking" distribution in the limbs. Clarke and Robinson (1956) found this in three out of 120 cases of cervical myelopathy, and, as in the cases here described, it was associated with posterior column modality impairment. In both Cases 1 and 2 the sensory symptoms and signs were more marked in the upper limbs, and Daniels (1956) has described similar cases with cervical-cord lesions in which the same observations were made; his second case resembles the cases now reported both clinically and pathologically. The prominent sensory symptoms and signs are common to these cases and suggest involvement of the posterior portion of the spinal cord, and the posterior columns in particular. It is, however, difficult to correlate these clinical findings with the usually accepted pathogenesis of the cord lesion in cervical myelopathy, for anteriorly placed compression would be expected to produce more evidence of pyramidal-tract damage.

There has been a good deal of discussion concerning the aetiological factors in chronic cervical myelopathy secondary to spondylosis, and it seems likely that several exist and are of varying importance in different cases. One of them, first suggested by Taylor (1953) and more recently by Schneider *et al.* (1954), Daniels (1956), and Bradshaw (1957), concerns the role of the ligamentum flavum which forms the posterior wall of the cervical spinal canal. In some elderly persons there is a permanent corrugation of this ligament related to the degree of disk degeneration, and when the neck is extended protrusion into the spinal canal is enhanced so that distortion of the posterior surface of the spinal cord occurs. Although visible at necropsy, it may have produced no symptoms during life. The anterior lesion produced by the extension of disk, osteophyte, and posterior longitudinal ligament into the spinal canal is likewise increased by neck extension and may also be symptomless. Thus either lesion may be silent when alone or at different levels, but if they are considerable and opposite each other the cord will be caught between two potent cord-compressing structures whenever the neck is extended, and a very severe degree of cord destruction may result (Clarke and Little, 1955). An exact correlation between the course of the disease and the known pathological findings is, however, notoriously difficult. The former is no doubt dependent upon the relative size of the anterior and posterior lesions as well as upon the other aetiological factors which have been postulated to account for the complex clinical picture characteristic of cervical myelopathy.

The myelograms in both Cases 1 and 2 demonstrated the two lesions very well, for in each there was a break in the column of radio-opaque material when the neck was in extension, but which was less apparent with the neck in a flexed or neutral position. Anteriorly a filling defect was readily seen, but posteriorly there was an equally significant one, shown best by Fig. 1 on the Special Plate.

The prognostic and therapeutic aspects of the cases described here are also of interest and importance. The benign course of the disease is demonstrated, but it is possible that, if serious cord compression is intermittent and occurs only with extension movements of the neck, a severe clinical picture would not be expected initially. Spondylosis, dependent as it is upon degeneration of the ageing intervertebral disk, is probably always progressive, and aggravation of the present state is therefore likely, although this advance may be very slow and at times imperceptible.

Despite the absence of active treatment, such as neck immobilization or surgery, the patients have each reported improvement, although objectively there has been little change. While the subjective improvement could be explained by the patients' becoming more attuned to their symptoms, there has nevertheless been no recent increase in signs. The first patient has stopped heavy work, and this is a well-recognized method of producing a temporary arrest or improvement. The importance of careful observation in this condition before advising surgical treatment is obvious. Should their condition deteriorate the patients will be advised to wear a collar, and if this is not effective a simple laminectomy with division of the dentate ligaments will be considered. In view of the nature of the lesion demonstrated, such an operation would be expected to give some relief.

Summary

Two cases of chronic cervical myelopathy due to spondylosis are described. Each had a clinical picture which was initially ascribed to peripheral neuropathy, but it was eventually possible to demonstrate compression of the cervical spinal cord in both of them. The responsible lesion had two components, the more usual one involving the anterior surface of the cord, and a posterior one due presumably to corrugation of the ligamentum flavum and explaining, perhaps, the predominance of sensory features in these cases. Conservative treatment has led to symptomatic improvement, and the benign and lengthy course of this condition in some patients is emphasized.

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AN UNUSUAL SITE FOR GRAVITATIONAL ULCERS

SOME OBSERVATIONS ON A CASE OF DEEP-VEIN THROMBOSIS

BY

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[WITH SPECIAL PLATE]

Gravitational ulcers, a sequel of deep-vein thrombosis, are usually situated around or above the malleoli where perforating venous channels can be found (Cockett, 1955). Ulceration between the toes is uncommon, though it is described after sympathectomy for persistent gravitational ulceration (Linton, 1953).

Following thrombosis of the popliteal or superficial femoral veins, blood may return from the foot either through recanalized, and therefore valveless, deep veins or through the superficial veins. These superficial veins may already be varicose with incompetent valves, or may become incompetent as they dilate. There seems to be no evidence of a compensatory deep venous collateral circulation developing in any way comparable to the collateral circulation developed after an arterial blockage.

The common sequel of venous engorgement leading to ulceration is usually prevented by a strong elastic support, particularly the "blue line" elastic bandage. The case described here demonstrates how a "blue line" bandage promoted healing of the malleolar ulceration, but caused severe congestion of the toes with eventual ulceration. Evaluation of the clinical findings and a venogram led to the discovery of a satisfactory method of elastic support.

Case Report

A machine attendant aged 35 complained of repeated painful ulceration between the toes of his left foot for the past twelve months. He had lost three months from work because of this. At the age of 15 he suffered a slipped epiphysis in his left hip, and when he was 22 he began to have pain in the same hip; this gradually got worse until January, 1953, when, at the age of 32, he underwent a subtrochanteric osteotomy. After the operation he was immobilized in a plaster spica for six months. One week after the plaster was removed he developed a deep-vein thrombosis in the left leg. This was treated by rest and support, but later when he was walking around on crutches the leg became swollen, and by December, 1953, five months after the thrombosis, he had areas of ulceration on the outer side of the ankle. This was treated with "blue line" elastic bandaging, and the malleolar ulcers healed and remained so. The bandages were comfortable, but he did notice that his toes were congested. Discoloration of the skin between the

toes became very marked by December, 1955, and in the next month one ulcer began between the first and second toes and another on the dorsum between the fourth and fifth toes. Since then he had been resting with the leg elevated for two months, and the ulcers were healed on admission to hospital.

Examination showed him to be a well-built man with 2 in. (5 cm.) real shortening of the left leg. The leg was in good position with no fixed flexion deformity. The only movement possible in the hip was 30 degrees flexion and 10 degrees abduction. There was a well-healed osteotomy scar. Below the knee the leg was swollen and showed many superficial varicosities. Areas of healed ulceration with supple scars were seen above the lateral malleolus, between the first and second toes, and on the dorsum of the foot. Dorsalis pedis and posterior tibial pulsation was present on both sides. The temperature of both feet was the same. The valves in the dilated superficial veins were incompetent, showing rapid retrograde filling. The application of a tourniquet to prevent superficial venous return was tried and the leg then exercised (Perthes's test). There was some discomfort and congestion of the leg with the tourniquet around the mid-thigh; painful congestion was marked when it was applied around the knee, but with the tourniquet at the mid-calf level the leg could be exercised with comparative comfort.

Investigations.—Phlebography was performed (Fig. 1) by injecting 70% diodone into the long saphenous vein on the dorsum of the foot. A tourniquet had been applied above the ankle to occlude the superficial veins, and a crepe bandage from the ankle to the groin to keep all the superficial veins above empty (Muir *et al.*, 1954). Screening and films showed marked narrowing of the popliteal vein at the level of the tibial condyle due to recanalization of the thrombosed segment. No deep anastomotic channels are seen.

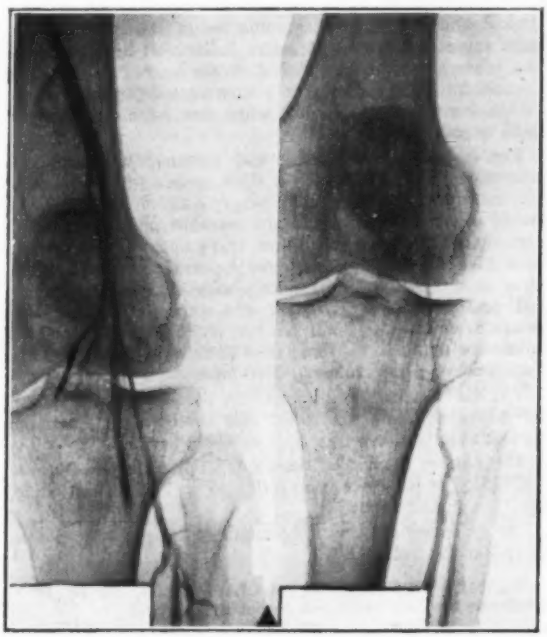

FIG. 1.—Venogram showing narrow recanalized popliteal vein. Left-hand film, taken after Valsalva manœuvre, shows normal vein above obstruction and retrograde filling of veins from gastrocnemius.

Interpretation and Treatment

The narrowing of the deep veins appeared to be confined to the popliteal vein, so that blood returning from the foot had either to pass through this narrowed segment or to return via the superficial veins. It was thought that by applying an elastic bandage up to the knee, and so occluding the superficial venous "by-pass," the return of blood from the leg and foot was impaired, and that the congestion led to discoloration and ulceration below the elastic support—that is, on the dorsum of the forefoot and toes. That some sort of support around the ankle at the site of the perforating veins was required had already been seen, as malleolar ulceration had once occurred. It was therefore decided to apply support up to the mid-calf, as suggested by the Perthes test, in the hope of allowing blood to flow past the narrowed popliteal vein through perforating and superficial veins. Elastic bandaging to this level seemed comfortable, but was difficult to keep in place. A mid-calf elastic stocking was therefore made with a bone support to prevent its slipping down (Fig. 2).

FIG. 2.—Half calf-length elastic stocking with "bone" supports.

The patient was discharged and returned at once to his work. Nine months later he remains comfortable and there is no sign of ulceration or of increasing skin pigmentation, either on the foot or above the upper limit of the stocking. It is too early yet to say that ulceration will be prevented, but the patient is comfortable and says he experiences none of the congestion that he felt before when supported up to the knee.

NOTE.—The phlebogram showed that the veins above the narrowing were of normal calibre and had competent valves; it is, however, interesting to observe the way in which the otherwise normal femoral vein has been "concertinaed" owing to the shortening of the limb caused by an osteotomy (see Special Plate).

Summary

A patient with popliteal-vein thrombosis developed ulceration above the lateral malleolus, which was treated successfully with an elastic bandage. Although the first ulcers healed, severe ulceration began on the dorsum of the forefoot and in the interdigital spaces.

Interpretation of the physical and radiological signs led to the construction of a mid-calf-length elastic support, which has proved successful so far for nine months.

I should like to thank Mr. A. J. H. Rains for his permission to publish this case.

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The Central Middlesex Research Prize for 1958 has been awarded to Dr. DAVID PHEAR.

Medical Memorandum

Tuberculosis of the Vulva

Tuberculosis of the vulva is rare in spite of the prominence given to it in gynaecological textbooks. It was first described in 1881 (Bates and Rucker, 1944), and in 1915 Bulkley collected 71 cases from the literature. By 1949 Pardini found that only 100 cases had been reported, 11 of them primary lesions. According to Mathew (1949) genital tuberculosis is found in 0.2 to 2.0% of all gynaecological cases, and in 1 to 2% of these the external genitalia are involved.

Symptoms of pruritus, offensive discharge, dysuria, dyspareunia, and painful defaecation may be present. The lesions are either ulcerative or hypertrophic in the ratio of 10:1. Speiser (1942) describes three types of ulceration: lupus, scrofulodermal, and a third type presenting as a nodule which breaks down to form a painful tender ulcer with undermined edges, a granulating base, and dirty yellow exudate. The present case is of the latter type.

Suppuration and ulceration of inguinal lymph nodes sometimes occurs and biopsy may be of diagnostic value. Microscopy of the vulval ulcer often reveals typical tubercles, but the bacillus may not always be identified. In very few reported cases has guinea-pig inoculation been employed.

Additional endometrial biopsy for histology, culture, and guinea-pig inoculation should be carried out and the disease sought for in the urinary, gastro-intestinal, and pulmonary tracts, as in most cases the vulval condition is secondary to disease of these other sites.

The rarity of the primary form is due to the effective barrier raised by the squamous epithelium. Five cases of primary tuberculosis of the vulva were described by Schmid (1940), in three of which the female had been infected as a result of coitus with a male suffering from tuberculous epididymo-orchitis. Nilson (1949) described a further case in which the ulcer appeared in a Mantoux-negative virgin within a month of coitus, and quoted five similar cases. Jameson (1935) and Nilson (1949) present experimental evidence in animals in confirmation of the venereal basis for the primary lesion. However, in its occurrence in children, mentioned by Bates and Rucker (1944) and Pecker (1948), the source of infection was the fingers of the attendants or the floor.

Treatment has been that of the disease in general, and includes sanatorium treatment, improvement of the general health, calciferol, and a simple radical excision of the vulva with block dissection of the inguinal glands in certain cases.

Only a few cases have been reported since the advent of streptomycin. Benjamin and Charnock (1949) reported the first case successfully treated and cured in six weeks using streptomycin, 1 g. daily; and Mathew (1949) had a similar case which took two months to heal. Corbet (1953), in this country, found no improvement in the condition of a hypertrophic lesion in spite of prolonged treatment with 127 g. of streptomycin, and finally obtained a cure by vulvectomy. Soichet, Posner, and Hogans (1955) also had to resort to surgery for a hypertrophic lesion unsuccessfully treated with streptomycin and isoniazid (isonicotinylhydrazine).

CASE REPORT

A nulliparous woman aged 37, married several years, was referred on March 24, 1955, to the venereological department with pruritus vulvae and rectal discharge of six weeks' duration, and, in the last three weeks, frequency of micturition and dysuria, with the development of pimples on the vulva and perianal region which later ulcerated. The only previous illnesses admitted to were myasthenia gravis, for which a thymectomy was done in 1951, and epilepsy. Periods of four days' duration and moderate loss occurred regularly every 28 days.

She was a frail poorly-looking woman who admitted to some loss of weight in the previous six months. There were several punched-out circular ulcers with undermined edges and granulating bases involving the clitoris, the natal cleft, and buttocks, and one in the anus extending for about an inch (2.5 cm.) into the anal canal. There was a rectal discharge, and small shotty glands were palpable in both groins. A provisional diagnosis of chancroid or tuberculosis was made.

Intracellular diplococci were demonstrated in the rectal pus, but no acid-fast bacilli were seen. Culture of the vaginal and rectal discharges failed to grow either the gonococcus or the tubercle bacillus, and the Wassermann and Kahn reactions and the gonococcal fixation test were all negative. In view of these findings it was concluded that the patient was suffering from rectal gonorrhoea and possibly an atypical form of chancroid. To avoid masking the presence of concomitant syphilis and also because of its specificity for chancroid, streptomycin, 1 g. intramuscularly daily, was given for four days, and sulphadiazine, 1 g. t.i.d., for a week.

By April 5 the patient felt better, but the vulval ulcers were unchanged and intracellular diplococci were still present in the rectal pus. In view of this, chlortetracycline, 250 mg. q.d.s., was prescribed, but gastro-intestinal side-effects necessitated withdrawal of the drug after two days. She reattended on April 14 complaining of a cough, and clinical and radiological examination of the chest at this stage revealed bilateral extensive infiltration of both lungs and tubercle bacilli were found in the sputum. She now confessed to having been previously treated for lung tuberculosis from 1937 until 1945, when the lesion was thought to be quiescent.

The patient was admitted, and treatment consisting of streptomycin 1 g., P.A.S. 15 g., and isoniazid 300 mg. daily was instituted. On April 28 a biopsy excision of one of the vulval ulcers was performed and endometrial curettings for histological examination, culture, and guinea-pig inoculation were taken. Histologically the appearance of the vulval ulcer was typical of tuberculosis with characteristic giant-cell and epithelioid systems, and tubercle bacilli were demonstrated by the Ziehl–Neelsen technique. Section and culture of the endometrium failed to show tuberculosis, and the guinea-pig unfortunately died prematurely.

The vulval ulcers had completely healed within a month on antituberculous treatment, and three weeks later the patient's sputum was free from tubercle bacilli.

The patient discharged herself from hospital on October 23, 1955, but has since been followed up at the chest clinic, and has remained well.

No evidence of genital tuberculosis or gonorrhoea was found in the husband.

We thank Dr. C. S. Nicol, Miss L. E. Hurter, and Dr. H. J. Anderson for their permission to publish this case.

J. CROSSLEY, F.R.C.S., M.R.C.O.G.
O. A. N. HUSAIN, M.D.

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Reviews

OPERATIVE SURGERY

Operative Surgery. Under the general editorship of Charles Rob, M.D., M.Chir., F.R.C.S., and Rodney Smith, M.S., F.R.C.S. Volume 4: Part VI—Head and Neck and Clearance of Lymph Nodes (pp. 164); Part VII—Vascular Surgery (pp. 144); Part VIII—Endocrine Glands (pp. 66). Volume 5: Part IX—Orthopaedic Surgery (pp. 366). Volume 6: Part X—Hand (pp. 105); Part XI—Amputations (pp. 71); Part XII—Plastic Surgery (pp. 131); Part XIII—Gynaecology and Obstetrics (pp. 123). (Illustrated. Volumes 4, 5, 6—£5 10s. each volume.) London: Butterworth and Co. (Publishers), Ltd. 1957–8.

The second three volumes of this monumental work follow lines similar to those adopted in the earlier series. Volume 4 deals with operations on the head and neck, the endocrine glands, and the blood vessels. The section on arterial aneurysms has been written by Professor Rob himself; the pictures are clear and the descriptions lucid and concise, but we should imagine that most surgeons would like to watch an experienced master at work before they tried these operations.

Volume 5 is entirely devoted to orthopaedic operations, and 16 different orthopaedic surgeons contribute to this elaborate section. All common and many rarer procedures are described and profusely illustrated. In looking through this volume I could not help wishing from time to time that it had been possible to state what was the average functional result as compared with that obtained by the older and less complicated methods.

Volume 6 contains an extremely important section on the surgery of the hand which well repays study, and another in which amputations are very concisely and efficiently described. The editors had the inestimable assistance of Sir Gordon Gordon-Taylor in the accounts of the forequarter and the hindquarter amputations. The final section on gynaecological and obstetrical operations is particularly well illustrated.

ZACHARY COPE.

MATHEMATICAL EPIDEMIOLOGY

The Mathematical Theory of Epidemics. By Norman T. J. Bailey, M.A. (Pp. 194+viii. 36s.) London: Charles Griffin and Co. Ltd. 1957.

The mathematical theory of epidemics has made great progress in recent years, thanks to the work of such men as M. S. Bartlett, D. G. Kendall, and the writer of this book. Following on a historical sketch of mathematical epidemiology and some discussion of epidemiological principles, the book contains chapters on deterministic theory, the two main kinds of stochastic theory—continuous infection models and chain binomials—the measurement of latent and infectious periods, recurrent epidemics and endemicity, and on the detection of infectiousness. The final chapter sums up the present position of the theory in relation to its application.

The distinction between deterministic and stochastic mathematical models of epidemics is fundamental. In a deterministic model the future state of the epidemic process can be determined precisely, given the initial numbers of susceptibles and infectious individuals, together with the attack, recovery, birth, and death rates. Deterministic theory goes back to the work of Hamer at the beginning of the century, followed by the much more definitely mathematical work of Ross and Soper, and the later collaborative work of Kermack and McKendrick. A stochastic (or probability) model, on the other hand, has a chance element inherent in its structure; from it can be deduced, not the precise state of the epidemic at any future time, but the probability of each of the possible states. With one brilliant exception, stochastic epidemic theory has been developed in the last 10 to 15 years. The exception was McKendrick, who, in a most remarkable but for many years almost unknown paper (1926), anticipated many of the modern developments. Greenwood's chain binomials (1931), which often provide useful models for the distribution of household infections, are also stochastic in character.

Stochastic models have greater generality than deterministic models. In theory, where one of the latter is satisfactory we could always find one of the former which would also be satisfactory; the converse is not true. However, the mathematical difficulties in dealing with stochastic models can be formidable. The author summarizes the position on these lines: Deterministic models are sometimes satisfactory for describing the general character of epidemics which begin in large groups with only small numbers of initial cases. The general prediction of an initial rise and subsequent fall, provided that the initial number of susceptibles exceeds a certain threshold value, is in broad agreement with observation. However, when a deterministic model is used for studying the problem of recurrent epidemics in large communities it is found that the waves predicted are subject to a heavy damping which does not occur in practice. The corresponding stochastic models are free from this defect. Further, they predict the phenomenon of fade-out of infection in communities below a certain critical size, which is actually found to occur in practice. Although judiciously chosen models may give considerable insight into large-scale phenomena, we may be unable to achieve anything sufficiently precise to justify statistical tests of goodness of fit.

In handling epidemic processes in small groups, especially those of household or classroom size, probability treatment is essential. . . . Where the study of small groups is concerned, much more work is required in the development of various models for a wide range of diseases. Thus chain binomials and the modification with latent and infectious periods have been investigated largely in the context of measles, for which reliable data are relatively more abundant than for other infections. It is suspected that a continuous infection model would be more appropriate for diphtheria and scarlet fever, for example, but no exact tests have been made.

The author thinks that it is undesirable that biometrical investigation of the type envisaged should continue along largely mathematical lines for any length of time without adequate checking from observational data. The success already achieved with measles suggests that it would be eminently worth while making special efforts to this end with household data for a wide variety of diseases. He has some useful remarks to make on means for attaining this end.

J. O. IRWIN.

HAEMOLYTIC DISEASE OF NEWBORN

Comparative Aspects of Haemolytic Disease of the Newborn. By G. Fulton Roberts, M.A., M.D. (Pp. 199+xi. 17s. 6d.) London: William Heinemann Medical Books Ltd. 1957.

Haemolytic disease of the newborn has been recognized in man since the middle of the seventeenth century, while severe jaundice of the newborn foal was first described in 1774. Haemolytic disease in the pig has been noted only during the last ten years, and in this animal it has been produced experimentally as well as observed clinically. Much experimental work on hetero- and iso-immunization in other animals, such as the guinea-pig, rat, dog, rabbit, and mouse, has been described. Dr. Roberts, in a book which will appeal to practitioners of human and veterinary medicine alike, has collected this information together to compare the different clinical and serological manifestations of a condition in which great advances have been made in the last two decades. It is clear that the blood groups in animals are not nearly so well worked out as those in man, and this gap in our knowledge has perhaps hindered the experimental study of haemolytic disease of the newborn. The way in which maternal antibodies gain access to the foetal antigens in the different species is closely considered, and there is a wealth of odd and interesting facts, such as

that haemolytic disease in the pig may be due to swine-fever vaccine; this is made from pooled pigs' blood, in which it is thought that an antigen present in the blood of Large White pigs can immunize sows of the Saddleback breeds. If a mare or a sow produces offspring affected by haemolytic disease of the newborn one just discards this dam from the breeding stock, and many a human practitioner will wish the problem could be as simply dealt with in his patients.

The author is to be congratulated on producing another book as good as his earlier one on the rhesus factor. The subject-matter is written almost as a series of essays in clear and comprehensible language, and in order not to obstruct the flow of the reader's thought the earlier and more obscure literature is excluded from the text and assembled in a fascinating appendix.

I. A. B. CATHIE.

RADIATION AND HUMAN HEREDITY

Effect of Radiation on Human Heredity: Report of a Study Group Convened by W.H.O. Together with Papers Presented by Various Members of the Group. (Pp. 168. 20s.) Geneva: World Health Organization. 1957.

In 1957 W.H.O. convened a study group at Geneva to discuss the effects of radiation on human heredity. The group was drawn from geneticists from countries other than those with existing national committees studying the same problem. Other experts were invited to indicate the lines of research which should be followed in order to increase our understanding of the effects of radiation on human heredity. In this book is presented the formal report of the group together with the papers presented by the various members.

IVOR G. WILLIAMS.

CHILD PSYCHIATRY

Child Psychiatry. By Leo Kanner, M.D. Prefaces by John C. Whitehorn, M.D., Adolf Meyer, M.D., LL.D., and Edwards A. Park, M.D. Third edition. (Pp. 777+xxiv. 63s.) Oxford: Blackwell Scientific Publications. 1957.

This work is still the only textbook on child psychiatry of international status, and, entering on its third edition, it discloses the great advances that have been achieved in this subject in the last 20 years. The expansion of the subject consists not solely in the additional facts regarding child psychology and child conduct disorders—of both physical and psychological aetiology—but in the substantial change in both emphasis and attitude. Much more space is given to the psychological processes involved, and this means that a greater accent has been laid upon the human relations than upon the bare clinical features of the problems as they present themselves. Basic orientation occupies 150 pages, and this covers the broad psycho-physical concomitants, including intelligence, personality, and attitude. The latter covers not only the posture, as it were, of child and parent, but that of the observer. The section in clinical considerations is of particular value to the student approaching the subject from general paediatrics and from the angle of formal psychology. Symptoms are seen as signals and indicators rather than as phenomena basic to the disorder.

History-taking and diagnostic aids—for example, projection tests, play, and expressive activities—are succinctly and usefully outlined without any doctrinal bias, while doing justice to the various psychopathic theoretical approaches.

The phenomenology naturally covers a large section and brings psychiatry and paediatrics into rational and methodological relation to each other. Here the various organic anomalies have brief but clear-cut references: the epilepsies are adequately dealt with for so comprehensive a textbook. The psychosomatic problems of childhood are issues which bring together the mental and the physical, a nexus which is so close in early life that any dichotomy would be misleading. Dr. Kanner has been wise in interpolating this section between phenomenology and the behaviour disorders. Nevertheless the total lay-out of this valuable textbook illustrates the fact that classification of child problems has scarcely passed beyond the Linnaean stage of scientific development. The psychopathologist *pur sang* would have patterned the book otherwise, but Dr. Kanner has shown wisdom in not stepping beyond the inductive method of scientific procedure by endorsing theories not fully established.

EMANUEL MILLER.

COUNTRY PRACTICE

Country Practice. By Hubert Bagster. (Pp. 187. 15s.) London: Andre Deutsch. 1957.

Dr. Bagster has drawn on his experiences and on his imagination to tell us about country practice on the English side of the Welsh border. His stories are good and he tells them with wit and the authority that comes with accurate observation and a real love of his subjects—the countryman and his way of life. As befits a general practitioner, his stories are about people and their misfortunes and illnesses rather than about disease. Dr. Bagster is an exponent of social medicine, a modern term for an aspect of medicine that has been practised by general practitioners for a hundred years or more. Unlike most medical writers of the present day, he describes the impact of the National Health Service on his practice with restraint and good sense, and he obviously respects his old teachers. He is not ashamed to admit that he is sometimes wrong, and he is willing to learn even from an unqualified nurse.

It must be unusual for a practitioner to find three potential poisoners in his practice in one lifetime. Some of the stories are like fairy stories—true but not to be taken literally. After all, the difference between a fairy story and a real-life story is that the fairy story is complete and tidy, whereas in real life the story is incomplete and there are a lot of loose ends.

This is a most readable book by a delightful person which will be enjoyed and appreciated by his colleagues as well as by a wider public.

C. W. WALKER.

From Magic to Medicine, by Ritchie Calder, is a pictorial history of medicine from primitive times to the present day. Profusely illustrated, largely in colour, this provides an ideal introduction for those who know little of medicine and its development from ancient magic potions and ceremonies to sulphonamides and delicate surgery. Simple anatomy and physiology are explained, with the gradual growth of man's knowledge of his own body. The great landmarks in the conquest of disease are related to the general development of medical research; and in modern medicine the Salk vaccine and cobalt therapy of cancer are included, as well as a survey of the work of W.H.O. in Asia and Africa. The book is published by Rathbone Books, 37, Hertford Street, London, W.1, price 17s. 6d.

The eleventh edition of *Taylor's Principles and Practice of Medical Jurisprudence*, edited by Sir Sydney Smith and Dr. Keith Simpson, is completed with the publication of Volume II (J. and A. Churchill, Ltd., London; 80s.). Recent changes in the law and advances in forensic pathology have necessitated a more radical revision than usual. Many new cases are cited. Volume II deals with sexual medical jurisprudence and with toxicology.

Vol. 10 of the *Selected Papers from the Institute of Cancer Research, Royal Cancer Hospital, and from the Royal Marsden Hospital* is now available from the Institute (Fulham Road, London, S.W.3). In this volume are reproduced 83 papers on cancer and related subjects published during 1955.

In the seventh edition of *Hewer's Textbook of Histology for Medical Students*, edited by C. L. Foster, M.Sc., Ph.D., the sections on the cell, connective tissue, liver, and hypophysis have been extensively revised. The book (438 pages; 27s. 6d.) is published by Heinemann Medical Books, Ltd., London.

The Carbohydrates: Chemistry, Biochemistry, Physiology, edited by Ward Pigman, is a revised and expanded version of *Chemistry of the Carbohydrates*, published in 1948. The 14 contributions by various authorities include two new chapters on photosynthesis and metabolism and on nutritional aspects. The book (902 pages; $20) may be obtained in this country from Academic Books, Ltd., London.

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SAFER DIAGNOSTIC RADIOLOGY

Radiation will reduce the life-span of experimental animals, though there is no evidence that doses comparable to those used in diagnostic radiology have any such influence. S. Warren[1] has put forward figures purporting to show that American radiologists may have had their lives shortened as a result of being exposed to ionizing radiations, though his conclusions have been challenged.[2] Radiation can cause leukaemia in animals, and evidence from several sources —a study of the causes of death of American radiologists,[3] and follow-up of Japanese survivors of atomic bombing and of patients given radiotherapy for ankylosing spondylitis[4 5]—leaves little doubt that irradiation is a cause of leukaemia in man. Whether there is such a thing as a threshold dose remains uncertain, and therefore the possible danger of diagnostic radiology in this connexion is still a subject for speculation. The preliminary report of Alice Stewart and her colleagues[6] suggested that exposure of children to *x* rays during their prenatal life may be an aetiological factor in the development of leukaemia and other neoplastic diseases in infancy and childhood. W. L. Russell[7] and L. B. Russell[7 8] have shown that in experimental mice doses of 25 r or more could lead to demonstrable changes in foetuses irradiated during the period of major organogenesis. They advised that radiography of the pelvis should be restricted to the post-menstrual fortnight so as to avoid the possibility of irradiating the foetus in an unsuspected pregnancy. This would seem to be a wise precaution to take: no known case of early pregnancy should be irradiated if it can be avoided.

Apart from accidents resulting in gross overexposure, the most important potential danger of diagnostic *x* rays is the production of mutations. *X* rays are known to cause mutations in experimental animals and in plants, and there is little doubt that they can cause them in man. Future generations may therefore be affected by mutations induced by irradiation of a patient's gonads. In 1952 R. W. Stanford, S. B. Osborn, and A. Howard[9] reported the results of a pilot investigation into the gonad dose of radiation received by the population from diagnostic procedures. They estimated this to be about 5% of that received from naturally occurring radiations. Similar results were obtained in America[10] and Australia.[11] It was not until the publication in 1956 of the Medical Research Council's report entitled *Hazards to Man from Nuclear and Allied Radiations*[4] that there was any evidence to show that the previous estimates had been far too low. Basing their assessment on the published figures for the number of *x*-ray examinations carried out in National Health Service hospitals in the United Kingdom, the authors of this report concluded that, in the population up to 30 years of age, diagnostic procedures contributed a dose equivalent to at least 22% of that from natural radiation. Several authorities have suggested that this estimate is also too low,[12–15] and reports from Sweden and the U.S.A. have mentioned estimates of 100% or more as being not unrealistic. In the United Kingdom a committee under the chairmanship of Lord Adrian is at present collecting evidence on which reliable conclusions can be drawn. The Medical Research Council's report[4] stated that "those responsible for authorizing the development and use of sources of ionizing radiation should be advised that the upper limit which future knowledge may set to the total dose of extra radiation which may be received by the population as a whole is not likely to be more than twice the dose which is already received from the natural background; the recommended figure may indeed be appreciably lower than this." Though there are many uncertainties in the present situation most would agree that everything possible should be done to avoid the induction of genetic changes by radiation and that the contribution of diagnostic radiology to the total dose of radiation received by the population is undesirably high.

Fortunately it should be quite possible to carry out the present volume of diagnostic radiology with a smaller dose of radiation than that used in the past.[15] In practice this means the elimination of all unwanted radiation. The smallest possible beam of radiation

[1] Warren, S., *J. Amer. med. Ass.*, 1956, **162**, 464.
[2] See annotation, *Brit. med. J.*, 1958, **1**, 1112.
[3] Lewis, E. B., *Science*, 1957, **125**, 965.
[4] Medical Research Council, *The Hazards to Man of Nuclear and Allied Radiations*, 1956, H.M.S.O., London.
[5] Court Brown, W. M., and Doll, R., "Leukaemia and Aplastic Anaemia in Patients Irradiated for Ankylosing Spondylitis," *Spec. Rep. Ser. med. Res. Coun. (Lond.)*, No. 295.
[6] Stewart, A., Webb, J., Giles, D., and Hewitt, D., *Lancet*, 1956, **2**, 447.
[7] Russell, L. B., and Russell, W. L., *Radiology*, 1952, **58**, 369.
[8] Russell, L. B., in *Radiation Biology*, 1954, **1**, part II, 861, "The Effects of Radiation on Mammalian Prenatal Development."
[9] Stanford, R. W., Osborn, S. B., and Howard, A., *Brit. J. Radiol.*, 1952, **25**, 387.
[10] Billings, M. S., Norman, A., and Greenfield, M. A., Report U.C.L.A. 340, 1955, University of California School of Medicine, Los Angeles.
[11] Martin, J. H., *Med. J. Aust.*, 1955, **2**, 806.
[12] Osborn, S. B., and Smith, E. E., *Lancet*, 1956, **1**, 949.
[13] United Nations Scientific Committee, *Brit. J. Radiol.*, 1957, **30**, 282.
[14] Laughlin, J. S., and Pullman, I., "Biological Effects of Atomic Radiation: Gonadal Dose Produced by Medical Use of X-Rays." Preliminary Report by National Academy of Science, Washington, D.C., 1957.
[15] Ardran, G. M., *Brit. J. Radiol.*, 1957, **30**, 436.
[16] Haybittle, J. L., ibid., 1957, **30**, 663.

just to cover the area under examination should be used, and the edge of the primary beam should be visible on all films. These precautions should be combined with the use of filters, the fastest films and intensifying screens, and the highest kilovoltage that will yield films of adequate quality for the particular examination. If possible the gonads should be directly protected by lead in the male whenever they might be in the direct beam of radiation or when they are close to the edge of the primary beam. Protection of the ovaries when they are in the direct beam is rarely possible. It is of the utmost importance to keep the edge of the beam as far away from the testes or ovaries as possible; the dose falls off considerably with every inch of increased distance between them and the edge of the beam.[16] If these measures are applied, and if the number and incidence of examinations is in fact similar to that estimated for the purpose of the Medical Research Council's report, it should be possible to reduce the genetically significant radiation to about half that described in the report as the minimum. The rigorous adoption of these simple principles in *x*-ray departments will depend on the establishment of good discipline. But a reduction in the mean dose to the red bone marrow of patients should certainly follow. On the assumption that there is no threshold for the induction of leukaemia, this lowering of the radiation dose should reduce to negligible proportions such risk as there may be of inducing leukaemia, and no one need forgo any necessary *x*-ray examination because of the radiation danger. The instruction of staff and the provision of suitable equipment must be proceeded with as fast as possible. In these efforts the British Institute of Radiology is playing a valuable part by encouraging the publication of work relevant to the subject and by making available reprints of papers which have appeared in its journal over the last ten years.

ANTIVIRAL CHEMOTHERAPY

In antiviral chemotherapy almost any compound which can be synthesized by an obliging chemist or picked out of the catalogue of some chemical firm may eventually come to trial. But, apart from miscellaneous work of this kind which is always going on, research at present is being concentrated on three classes of compound—namely, substituted benzimidazole ribosides, dicarbonyls, and thiosemicarbazones. However, since the field was last reviewed in these columns,[1] no antiviral compound has come into clinical use, and the work which has been published meanwhile is a voluminous catalogue of hopes, uncritical optimism, and eventual disappointment which has led to little in the way of solid achievement. It has been well reviewed by Weston Hurst and R. Hull[2]; their review covers 478 publications, none of which has yielded any antiviral compound of interest to the clinician.

I. Tamm and his collaborators[3 4] have studied a number of benzimidazole ribosides, which are structurally related to part of the molecule of cyanocobalamine. These substances were tested for antiinfluenzal activity by an *in vitro* method in which pieces of chorio-allantoic membrane were placed in a suitable medium containing the test substance in solution and then infected with the virus. After incubation the extent of multiplication of the virus was determined by carrying out haemagglutinin titrations on the supernatant fluid. The titres were lower than in control preparations from which the test substances were omitted, and in experiments with 5:6-dichloro-1-β-D-ribofuranosylbenzimidazole (D.R.B.), one of the most active compounds studied, a small reduction in haemagglutinin titre was achieved when the concentration was near the toxic level. H. M. Kissman and co-workers[5] were unable to demonstrate any therapeutic effect with D.R.B. in 73 mice infected with influenza virus. Tamm has also claimed that D.R.B. and related compounds can exert antiviral activity against the MEF-1 strain of poliomyelitis virus in monkey-kidney tissue cultures. However, the effect is slight, the effective antiviral dose is as high as one-third of the toxic dose, and once again Kissman and his colleagues have failed to confirm these claims. It may be concluded that benzimidazole derivatives do not at present offer any promise of yielding anything of clinical value.

A number of dicarbonyl compounds have been investigated by W. F. McLimans and co-workers.[6] The most active was β-ethoxy-α-ketobutyraldehyde hydrate (kethoxal), which had a virucidal effect on influenza and Newcastle disease viruses multiplying in fertile eggs. However, compounds of this class can react with amino-acids and destroy them; kethoxal and allied compounds consequently have a marked virucidal effect *in vitro*, and the apparent antiviral activity in eggs was therefore probably due to the inactivation of the virus while in contact with the test

[1] *Brit. med. J.*, 1954, **2**, 348.
[2] Hurst, E. W., and Hull, R., *Pharmacol. Rev.*, 1956, **8**, 199.
[3] Tamm, I., Folkers, K., Shunk, C. H., and Horsfall, F. L., *J. exp. Med.*, 1954, **99**, 227.
[4] —— and Nemes, M. M., *Virology*, 1957, **4**, 483.
[5] Kissman, H. M., Child, R. G., and Weiss, M. J., *J. Amer. chem. Soc.*, 1957, **79**, 1185.
[6] McLimans, W. F., Underwood, G. E., Slater, E. A., Davis, E. V., and Siem, R. A., *J. Immunol.*, 1957, **78**, 104.
[7] Liu, O. C., Malsberger, R. G., Carter, J. E., and DeSanetis, A. N., ibid., 1957, **78**, 214.
[8] Thompson, R. L., Minton, S. A., Officer, J. E., Hitchings, G. H., Wiener, F. P., and Hampil, B., ibid., 1953, **70**, 229.
[9] Bauer, D. J., *Brit. J. exp. Path.*, 1955, **36**, 105.
[10] Bock, M., *Z. Hyg. Infekt.-Kr.*, 1957, **143**, 480.

compound in the allantoic fluid, rather than to any interference with the process of virus multiplication. A somewhat similar compound, 1-γ-(*o*-chlorobenzyl)-δ-oxo-γ-phenylcaproic acid (caprochlorone), has been studied by O. C. Liu and co-workers.[7] This compound is not virucidal, does not affect the adsorption of virus, and is active against the PR8 strain of influenza virus in de-embryonated eggs. Caprochlorone is also active against influenza in mice, but only if the infecting dose of virus is small. It gives protection against a larger dose when the mice are also treated with γ-globulin.

After surveying the manifold endeavours in these fields which have so far yielded so little return it is a relief to turn to the thiosemicarbazones. The observations of R. L. Thompson and co-workers[8] on the antiviral effect of thiosemicarbazones in mice infected intracerebrally with a neurotropic strain of vaccinia virus have been extended by D. J. Bauer,[9] who has shown that isatin thiosemicarbazone has considerably greater antiviral activity than previously suspected. It will in fact protect mice against intracerebral infection with the enormous dose of 100,000 LD_{50} of virus when given in a daily dose of 1 mg.; moreover, a single dose of 0.5 mg. given 18 hours after infection will confer absolute protection against 100–1,000 LD_{50} of virus. Neurovaccinia in mice has admittedly no direct bearing on human disease, but now that the antiviral activity of penicillin and the tetracyclines has been abolished by a stroke of the pen by those unsympathetic systematists who have transferred the agents of the psittacosis–lymphogranuloma group to the order Rickettsiales, it may fairly be claimed that isatin thiosemicarbazone is the only really effective antiviral agent in existence at the present time.

Apart from slight activity against Rift Valley fever, isatin thiosemicarbazone is not active against other viruses; in particular, M. Bock[10] has found that it is inactive against ectromelia. This finding comes as a rude shock in view of the very close serological relationship and general similarity between ectromelia and vaccinia viruses. Bauer has suggested that isatin thiosemicarbazone is worth a clinical trial against smallpox, a virus which is equally closely related to vaccinia, but in view of the lack of activity against ectromelia it would clearly be premature to assume that this compound must necessarily be active against variola as well. However, it would be disappointing if such a powerful antiviral agent could not be put to some clinical use, and it is conceivable that it might find some application in the treatment of generalized vaccinia and post-vaccinal encephalitis, or in modifying the severity of primary vaccinations. In this connexion it is significant that mice treated with isatin thiosemicarbazone and infected with neurovaccinia show no signs of illness, but nevertheless develop a solid immunity.

One important conclusion to be drawn from the work on isatin thiosemicarbazone is that there is so far no reason to suppose that a chemotherapeutic agent can be found which will be active against all viruses. We cannot at present hope to be provided with a broad-spectrum antiviral substance. It is more probable that each virus will have to be fought and overcome separately, and the progress made so far suggests this may be a long process.

ARTIFICIAL RESPIRATION

The giving of artificial respiration without delay in emergencies raises some difficult problems,[1] many of them not truly medical. Joseph Clover stressed that, no matter what method is used, it must fail if the air passages are blocked either by foreign material or by an abnormal disposition of tongue, palate, and jaw. F. C. Eve always stressed this point and introduced a special whistle so that first-aid workers could learn to be aware of the movement of air into and out from the lungs, rather than merely carrying out the motions of artificial respiration by rote.

Recent important work by such investigators as H. G. Swann and M. Brucer[2] has suggested that in certain emergencies, such as acute asphyxia and drowning, a little air will do a lot of good if it is introduced into the lungs soon enough, but events march so quickly that a few seconds later even the most perfect artificial ventilation may be fruitless. This has led to the advocacy of immediate attempts at artificial respiration, and freeing the air passages has been regarded as an important but secondary objective.[3] However, emergencies differ and so do the circumstances. A patient poisoned by a long-acting non-volatile depressant may not be in instant hazard of his life, but unless good ventilation of the lungs is soon established and maintained, perhaps for hours, he may die. For him, a free airway and a thoroughly efficient technique of artificial ventilation seem essential. As to circumstances, a technique which is easy on a beach may be impracticable in a small boat or a mine. These considerations lead to a conflict, for success seems to depend on applying the right technique in the right manner, these depending on the nature of the emergency and the circumstances. Nevertheless, everyone wants to avoid equivocation

[1] *Brit. med. J.*, 1952, **2**, 273.
[2] Swann, H. G., and Brucer, M., *J. appl. Physiol.*, 1951, **3**, 479.
[3] Donald, K. W., *Brit. med. J.*, 1955, **2**, 155.
[4] Safar, P., Lourdes, A. E., and Elam, J. O., *New Engl. J. Med.*, 1958, **258**, 671.

and complexity in the advice given to first-aid workers, since indecision is usually fatal. When instruction must be given to the general public through posters compromise has to be accepted in the interests of essential simplicity and clarity. Certainty is impossible, and the best chance must be accepted.

"Mouth-to-mouth" artificial respiration has long been used on babies, and anaesthetists have practised it for many years on adults, both in the operating-room and in emergencies in the wards. A group of American doctors have for some time advocated a wider place for this technique, and in an important article[4] they give their reasons. In trials on anaesthetized and curarized volunteer subjects and patients the natural air passages were often found to be so obstructed that chest-pressure techniques were unsatisfactory unless a second person supported the jaw. Using the mouth-to-mouth method, a single operator could support the jaw and ventilate the lungs adequately. The authors recognize the aesthetic objections to the simple mouth-to-mouth technique—objections which may be of practical importance if they lead to hesitancy—and they suggest a simple device based on an oropharyngeal airway which they argue makes the procedure both more acceptable and more effective. On this basis they advocate the technique for ambulance and Red Cross personnel, beach guards, policemen, doctors, and nurses. Their views must receive serious consideration, particularly where they positively indicate the effectiveness of the mouth-to-mouth method, but it seems unlikely that their argument against the effectiveness of other techniques will go unchallenged.

SEXING OF TUMOUR CELLS

With the single exception of the germ cells, the cells of all tissues and organs of women carry within their intermitotic nuclei a distinctive hallmark of their sex in the form of a mass of deeply staining chromatin. It measures a micron or so in diameter and is usually plano-convex in shape, the plane surface lying against the nuclear membrane. In all probability this chromatin body is formed by the fusion of those portions of the two female XX chromosomes which retain, during the intermitotic period, the avidity for basic dyes which all the chromosomes develop during mitosis but the large majority lose during interphase. There is no proof that a much smaller chromatic mass present in a small minority of the nuclei of male cells has the same biological significance as the well-characterized mass of sex chromatin found in women.

Since 1949, when M. L. Barr and E. G. Bertram,[1] of the University of Western Ontario, discovered this mass of female sex chromatin in female cats, and K. L. Moore and Barr[2] in 1954 confirmed its presence in the tissues of women, a considerable number of human tumours have been examined to decide if the chromatin sex of the cells of a tumour is identical with the sex of its host. A review of the published work on this problem shows very clearly that the certain recognition in intermitotic nuclei of this mass of female sex chromatin, or, in short, the "Barr body," may present considerable difficulties.

In the first place a large proportion of the Barr bodies becomes unrecognizable unless the tissue is efficiently fixed in relatively thin slices within two to three hours after removal. Some observations by A. R. Sohval and J. A. Gaines[3] illustrate this difficulty. They examined 156 human tumours; 62 of these were benign growths occurring in women, and in 44 (71%) they failed to find female sex chromatin in the intermitotic nuclei. The material examined was part of a laboratory collection of sections, some of which were from specimens obtained by open operation. There must be some doubt whether all their material was adequately and rapidly fixed, for in the same year, using perfectly fixed material, Moore and Barr examined 65 benign tumours whose hosts were women, and found a high percentage of Barr bodies in the intermitotic nuclei of all specimens.

A second and more serious difficulty in the certain identification of the Barr body is directly related to the amount, and more especially the degree of dispersion, of deeply staining chromatin, other than sex chromatin, in the intermitotic nucleus. In nuclei usually described as vesicular the chromatin is so finely dispersed that by ordinary methods of observation individual particles are difficult to discern and the Barr body stands out with maximum prominence. It is remarkably easy, for instance, to "sex" the nuclei of cartilage cells and the cells in the zona fasciculata of the adrenal cortex. When the chromatin is coarsely dispersed as particulate masses it becomes increasingly difficult, and eventually impossible, to sex the nucleus as the particle size approaches and eventually exceeds that of the Barr body itself. The presence of particulate and deeply staining nuclear chromatin is characteristic of the normally pyknotic nucleus of the polymorphonuclear leucocyte, the lymphocyte, and the short-lived nucleus of the normoblast. W. M. Davidson and D. Robertson Smith,[4] for instance, reported that a Barr body could be found in only 1.5% of the polymorphonuclear cells in freshly fixed films of human female blood, the percentage of Barr-positive cells in the somatic tissues varying from 66 to 82%.

The presence of intranuclear masses of particulate chromatin in interphase nuclei is characteristic of cell populations in which the mitosis rate is increased and the intermitotic period correspondingly short, and nuclear "hyperchromatism" is universally regarded as a fairly safe indication of rapid growth in malignant

1. Barr, M. L., and Bertram, E. G., *Nature (Lond.)*, 1949, **163**, 676.
2. Moore, K. L., and Barr, M. L., *Acta anat. (Basel)*, 1954, **21**, 197.
3. Sohval, A. R., and Gaines, J. A., *Cancer (Philad.)*, 1955, **8**, 896.
4. Davidson, W. M., and Robertson Smith, D., *Brit. med. J.*, 1954, **2**, 6.
5. Tavares, A. S., *J. Path. Bact.*, 1957, **74**, 25.
6. Kimel, V. M., *Cancer (Philad.)*, 1957, **10**, 922.
7. Moore, K. L., Graham, M. A., and Barr, M. L., *Surg. Gynec. Obstet.*, 1953, **96**, 641.

tumours, in which it is usually associated with a high degree of anaplasia. A. S. Tavares[5] investigated the nuclear sex in a series of 53 undifferentiated carcinomata. The material was perfectly fixed, and in all cases the chromatin sex of the nuclei of the normal mesenchymal stroma cells of these tumours was identical with that of the host. In 22 of the 35 anaplastic cancers in women the sex of the hosts could not be correctly diagnosed by an examination of their tumour cells.

A recent preliminary study by V. M. Kimel[6] attempts to extend the sexing of tumour cells in another direction. He examined the routine histological preparations from 91 cases of human female breast cancer. These were taken from the files of a hospital laboratory, but no guarantee is given that the material had been rapidly fixed, and it is possible that the tissue obtained by open operation was not. A large proportion of the tumours was undifferentiated and the percentage of Barr-positive tumour cells in them was low. Twenty-six of these tumours had metastasized, and the patients had been treated by hormone therapy. On this basis this small group was divided into oestrogen-dependent (16 cases) and oestrogen-independent (11 cases). The percentage of tumour cells whose nuclei showed a Barr body was significantly higher in the oestrogen-dependent tumours than in those of the independent group. In view of the many pitfalls in sexing the cells of undifferentiated cancers it is doubtful if the results on so small a group of patients are suitable for statistical analysis. It is also worth remembering that investigations on pseudohermaphroditism have clearly shown that the chromatin sex of normal tissues is completely unaltered by the most marked aberrations in the sex-hormonal status of the patient.[7] In view of the importance of the claims put forward by Kimel it is to be hoped that he will continue his investigations.

RECOGNITION OF INTOXICATION

A common medical problem about which medical students learn very little, except in a rather incidental way, is the recognition of intoxication. Medical education would not be the same without its cases of Flatau-Schilder disease and left-to-right transposition of viscera, but the newly qualified doctor is less likely to be caught out by one of these than by a case of alleged drunk-in-charge. Exposed to cross-examination in the witness-box, he is apt to become embarrassingly aware of gaps in his knowledge of how alcohol affects the human mind and body. The subject is not all beer and skittles; it has its finer points.

A publication that many medical men have found helpful is a booklet entitled *Recognition of Intoxication*, published by the B.M.A. A committee under the chairmanship of Professor E. J. Wayne prepared it, and the first edition appeared in 1954. A second was required and is now available; it brings this important subject up to date. Practical advice is given on how to examine a person suspected by the police of being under the influence of alcohol. The booklet discusses the professional relationship between the doctor and the detained person, the doctor and the police, and the doctor and any other medical practitioner who may be called in. After setting out in detail a scheme for examining the detained person it gives advice on how the doctor should report his findings, if at all, and the extent of his obligations to give evidence in court. Some useful facts on alcohol in body fluids and methods of estimating it are included. Members of the medical profession may obtain the booklet free of charge on writing to the Secretary of the B.M.A.; to others the price is 1s. 6d. (by post 1s. 8d.).

MALNUTRITION AND PERIPHERAL NERVE DISORDERS

One of the earliest contributions to knowledge of the vitamins was that deficiency of vitamin B_1 was an essential cause of the abnormalities in nerve action described as "polyneuritis." Indeed, the classical contribution of Eijkman towards the discovery of vitamins, made near the end of the last century, was his recognition that polyneuritis in East-Indian chickens was due to a defect in their diet. From this conclusion it was a short step to find a parallel in the nervous symptoms typical of human beriberi. Years of clinical experience in the East, and particularly in prisoner-of-war camps during the second world war, confirmed the importance of vitamin B_1 in the prevention of beriberi, although there was some evidence that nervous syndromes of various kinds might also be caused by other dietary defects. Doubts cast by H. Luckner and R. Magun,[1] of Hamburg, on the validity of a relationship between polyneuritis and lack of vitamin B_1 may therefore cause surprise. As a preliminary to their pronouncements they criticize the term polyneuritis on the grounds that the nerves are not inflamed, and suggest a revision to "polyneuropathy." They then advance evidence which appears to exclude malnutrition as a cause of polyneuropathy, at least in Germany. Analysing the records of 191 patients with polyneuropathy admitted to a general hospital during the period 1943–55, they first direct attention to the wide variation in the incidence of cases in different years. In both 1945 and 1946 there were about 50 cases, as compared with 18 cases in 1944 and only 4 cases in all for the period 1950–3. Over the same years the incidence of many other diseases, typified by amyotrophic lateral sclerosis, showed only minor variations. As a second step all the cases of polyneuropathy were classified according to type—71 being essential, 65 post-diphtheritic, 35 toxic, and 20 in various other categories. The incidence of the two main types, essential and post-diphtheritic, was found to run parallel in the years under review, with the greatest numbers of both during the peak years 1945–6. Finally, the graph for the annual incidence of polyneuropathy, of all types, ran closely parallel to that for the incidence of diphtheria as notified in Hamburg. Attempts to correlate the incidence of either essential or post-diphtheritic polyneuropathy with the nutritional state of the patients were unsuccessful. No abnormalities could be found in the Röhrer

[1] Luckner, H., and Magun, R., *Germ. med. Monthly*, 1957 **2**, 97.

index (of height-weight relationship), nor did employment as a food producer or distributor confer protection. In extensive experiments with rats, subjected to both single and multiple deficiencies of vitamins and protein, the authors could find no evidence of peripheral nerve lesions.

Luckner and Magun make the point that wartime famine, in temperate regions, has not generally caused the high incidence of neuritic symptoms that would have been expected in the tropics. It is generally agreed that polyneuropathy is not always due to nutritional deficiencies, and therefore the administration of vitamin B_1 cannot be expected to confer benefit on all patients with this disorder treated in European hospitals. Large quantities of the vitamin may sometimes be expended with little justification. Beyond this point, however, few could be prepared to follow Luckner and Magun, who conclude from their findings that "neither the dietary deficiency of a single known factor nor a complex deficiency can any longer be considered the cause of any form of polyneuropathy, including that of beriberi." In the tropics the nutritional origin of beriberi seems indisputable, although secondary factors may sometimes complicate the picture. There is no solid evidence to divorce the nerve lesions from the rest of the syndrome, nor to displace vitamin B_1 as the central factor in treatment. Even in temperate regions the value of the vitamin for sufferers from alcoholic neuritis has been generally accepted. The failure of Luckner and Magun to induce nerve lesions in rats, and particularly in animals deprived of vitamin B_1 and vitamin E, is difficult to explain. Possibly the premature deaths of their animals may have prevented their maintenance on the deficient diets for periods long enough for the lesions to develop.

COMMONWEALTH UNIVERSITIES

The 1958 *Commonwealth Universities Yearbook*,[1] the 35th edition, appears in a new format and with several useful new features. The *Yearbook* is the principal publication of the Association of Universities of the British Commonwealth, a voluntary association of 114 universities and university colleges. Since it first came out, forty-four years ago, the *Yearbook* has established itself as an invaluable general directory for anyone wanting to know about university education in the Commonwealth. The new edition is a bigger and more handsome volume than its predecessors, and the universities are now listed by country as follows: Australia, Canada, Ceylon, Ghana, Hong Kong, India, Malta, New Zealand, Nigeria, Pakistan, Rhodesia and Nyasaland, Singapore and Federation of Malaya, South Africa, Uganda, the United Kingdom, and the West Indies. A short history of each university is included, together with the names and qualifications of its principal officers and staff, and information about the fees charged, degree regulations, and so on. A welcome innovation is the introductory essay on the university system in those countries with several universities. Details about the universities of the Republic of Ireland and the University of Khartoum are given separately in an appendix. The *Yearbook* is a most valuable service to higher education and the Commonwealth.

[1] *Commonwealth Universities Yearbook, 1958.* Published by Association of Universities of the British Commonwealth, 36, Gordon Square, London, W.C.1. Price £4 4s. (£4 6s. 6d.) by post.

W.M.A. APPOINTMENT

Our advertisement columns this week give the details of a new appointment to the head office of the World Medical Association in New York. The present secretary-general has intimated his intention to retire in the near future, and the W.M.A. therefore wishes to appoint a deputy secretary-general with a view to his succeeding to the senior post if he passes through the probation period successfully.

The vacancy advertised offers a unique opportunity for someone with administrative experience who wishes to promote the important work of the World Medical Association. Some 53 national medical associations constitute the membership of the World Medical Association, and the work of the secretary-general therefore entails a good deal of travelling, apart from attendance at the spring and autumn meetings held in different countries. In these days of intergovernmental agencies, when the fate of the medical profession all over the world can be so strongly influenced by policies formulated, for example, by the International Labour Office, by the International Social Security Association, and by the World Health Organization, it is essential to have an international organization which can represent the interests of the practising doctor and can make representations on his behalf to such bodies. Some few years ago, for example, the World Medical Association made an effective protest about the recommendation of an expert W.H.O. committee to the International Labour Office on the remuneration of practising doctors. In its early days the W.M.A. drew up an international code of ethics and the Declaration of Geneva, which have been now widely adopted all over the world. It organized the First World Conference on Medical Education held in London in 1953, and is now organizing the Second World Conference on Medical Education which is to be held in Chicago next year. The Proceedings of the First Conference are already widely regarded as a textbook in medical education. The W.M.A. has also published *World Medical Periodicals*, and in its organ, the *World Medical Journal*, published six times a year, records its activities and the results of its world-wide inquiries into the different aspects of professional life and work.

During the 10 years of its existence the W.M.A. has covered a good deal of ground, and its voice is listened to in other international organizations with respect. There is still much to do in the evolution of the policy of the W.M.A. which should offer great scope to an energetic medical man in his forties or early fifties who sees the need for proper representation of the interests of medical men at the international level.

We record with deep regret the death on May 28 of Lord Webb-Johnson, Consulting Surgeon to the Middlesex Hospital and a past president of the Royal College of Surgeons.

NUTRITIONAL PROBLEMS OF THE BRITISH CARIBBEAN

The third annual scientific meeting organized by the Standing Advisory Committee for Medical Research in the British Caribbean was held at the University College of the West Indies, Jamaica, on April 12 and 13. Food and its relationship to health and disease was the theme of the meeting, a subject which brought together agriculturists, veterinary workers, statisticians, research workers, nutrition experts, biochemists, pathologists, and clinicians.

Supplementing the Diet

The chairman on the first day was Professor A. C. FRAZER (Birmingham). Dr. H. C. MILLER, director of the Jamaican Department of Agriculture, the opening speaker, emphasized the need for increased agricultural production in underdeveloped countries and discussed some of the local difficulties. In Jamaica 75% of the land was mountainous, and only seven-eighths of an acre* per person was available for production, he said; in addition seven-eighths of the 200,000 farms were under 10 acres. This made scientific farming or even the introduction of improved methods difficult and time-consuming. Several papers were then read describing what is now being done in the British Caribbean to develop strains of cattle and vegetables suited to the local conditions.

A pilot nutritional survey of five low-income areas in Jamaica was reported by Dr. K. STANDARD, of the Government nutritional research team. Dental caries was shown to be related to the fluorine content of the drinking-water. The children were thin and underweight according to British and American standards. In British Guiana elementary school children had been studied by Dr. C. C. NICHOLSON in 1950, 1951, 1952, and 1958. Since 1954 a snack meal, consisting of skimmed milk, biscuits enriched with food yeast, and capsules of fish-liver oil, had been distributed to the schools. In the 1958 survey the effect of this was apparent. There had been a remarkable improvement in health, but there were still some skin, eye, and mouth lesions that might indicate slight residual vitamin A and B deficiency. The value of milk supplements was also stressed by Dr. L. HARNEY, of St. Kitts, who pointed out that there had been a significant drop in infant mortality compared with the "pre-milk era" which did not appear to be due to other causes. The failure of supplements of vitamin B_{12} and chlortetracycline to influence the growth of protein-deficient Jamaican children was reported by Professor I. F. S. MACKAY (U.C.W.I.).

Professor G. BRAS (U.C.W.I.) and Dr. D. M. BERRY (Jamaica) said they had produced veno-occlusive disease of the liver in calves by the administration of a toxic plant, *Crotalaria fulva*. Histopathologically the condition appeared to be closely similar to that seen in man. Dr. K. L. STUART (U.C.W.I.) reported on a series of 525 liver biopsies, stressing their diagnostic value. Dr. W. G. DOWNS (Trinidad Regional Virus Laboratory) reported on the immunity to Mayaro virus found in the inhabitants of a number of West Indian territories. It was confined to British Guiana and South-east Trinidad.

Megaloblastic Anaemia and Cardiovascular Disease

Sir GEORGE PICKERING took the chair on the second day, which was opened by Dr. W. E. MCCULLOCH describing pioneer work in nutrition in Nigeria and Jamaica over a period of 35 years. Dr. B. E. R. SYMONDS (Trinidad) then discussed malnutrition in infants. In 69% of the children dying between the ages of 1 month and 1 year, malnutrition was the sole or major contributory cause. Ignorance and apathy on the part of the mother were blamed for this. Dr. E. H. BACK and Professor G. BRAS (U.C.W.I.) reviewed ten patients who had recovered from kwashiorkor three and a half to five years previously. All were well, though five were below normal height and weight for their age, and four had hepatic enlargement. All the livers were histologically normal, including one that had shown fibrosis several years previously.

The occurrence of a nutritional megaloblastic anaemia in children of about 1 year of age was reported by Drs. J. MCIVER and E. H. BACK (U.C.W.I.). This had been noted in 50 children over a two-year period, 25.6% of all cases of malnutrition under the age of 2 years. In these patients the haemoglobin was less than in the usual case of malnutrition, being 7 g. per 100 ml. or less. All cases responded dramatically to the oral administration of folic acid (10 mg. per day). A variety of biochemical and electrophoretic observations in malnourished infants were discussed by Dr. L. WENT and Mr. G. HELLYER (U.C.W.I.), while a paper by Dr. B. B. G. NEHAUL (British Guiana) showed that in a group of East Indian patients a lower plasma albumin and a higher globulin level was found than might be expected in a comparable series in Britain or America. Feeding experiments on rats were reported by Mr. A. E. CHUNG (U.C.W.I.) and Mr. C. MENDES (M.R.C.).

Dr. J. A. TULLOCH (U.C.W.I.) commented on the low incidence of myocardial infarction in Jamaicans, and the theories relating atherosclerosis and diet were discussed. Dr. W. B. ROBERTSON (U.C.W.I.) demonstrated a high incidence of aortic atherosclerosis in the Jamaican comparable to that observed in New Orleans; on the other hand the relative infrequency of myocardial infarction appeared to approximate more closely to the incidence in Guatemala. Dr. W. B. ROBERTSON and Dr. H. G. DIXON (U.C.W.I.) reported on a combined clinical and pathological study of the maternal blood vessels at the placental site in normotensive and hypertensive pregnancies in women undergoing caesarean section. Marked changes in the vessels were noted in pre-eclampsia and in essential hypertension. Intimal proliferation or swelling, with considerable reduction or sometimes complete occlusion of the lumen, was found in the muscular and decidual vessels in the eclamptic or hypertensive woman. Dr. T. P. MAGEE (Trinidad) presented a preliminary report on factors that might be concerned in pre-eclampsia in Port of Spain. Dr. G. STIRLING (U.C.W.I.) said the Jamaican's adrenal glands were relatively small, the reduction in size affecting only the cortex and being particularly noticeable in the children.

The papers read at this meeting will be published in the medical press in due course.

*1 acre=0.4 hectare.

Reports of Societies

SLEEPING SICKNESS

SYMPOSIUM IN EDINBURGH

The Edinburgh Branch of the Royal Society of Tropical Medicine and Hygiene held a symposium on "Sleeping Sickness" on May 7 at the Edinburgh Royal Infirmary. Dr. A. M. GILLESPIE, the president, was in the chair.

Progress in West Africa

Dr. A. D. ROSS (Northern Nigeria) described the control of trypanosomiasis in Nigeria. There the disease was mostly encountered in the Northern Region, and was caused by *Trypanosoma gambiense*, transmitted mainly by the riverine tsetses *Glossina palpalis* and *G. tachinoides*. The disease was characterized by three stages, like syphilis. There might be an initial chancre at the site of inoculation three weeks after the fly's biting. This was followed by a stage of generalized infection, with malaise, apathy, intermittent headaches, anaemia, and almost always enlarged lymphatic nodes, particularly conspicuous in the posterior triangle of the neck (Winterbottom's sign). This stage lasted from one to several years before cerebral involvement became clinically apparent. The third stage with neurological changes might last for years, but by now trypanosomes

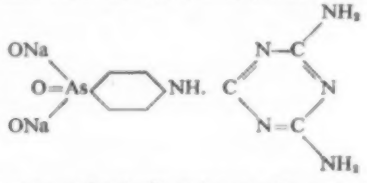
were scanty, and these patients probably did not constitute an important reservoir of infection for the tsetse flies.

Nigeria had a Sleeping Sickness Service with two main branches—medical, and fly control. Medical work was based on field surveys, treatment being carried out by mobile teams operating in conjunction with dispensaries staffed by trained personnel. Labour forces at mines were particularly exposed to tsetse flies at the height of the season for transmission, and here great success had followed chemoprophylaxis by pentamidine every six months. Mobile teams succeed in examining 80% of the population of an area; suspected cases, identified chiefly by neck palpation, were further investigated and confirmed cases treated. In the highly endemic Benue province an incidence of 250 cases among 20,000 people at a survey in 1956 had been reduced to 9 cases in 1958, following the annual treatment of all patients with a standard course of suramin and tryparsamide and annual prophylactic pentamidine for the remainder of the population. Fly control had been very successful in the drier northern areas, but the lush Benue valley was a much more difficult problem.

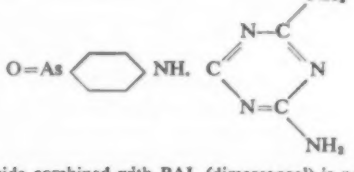
In 1935 examination of 400,000 people in Nigeria had revealed 80,000 cases of sleeping sickness: in 1956 the comparable figures were 2,822 cases among 1,800,000. While much of this reduction could be attributed to the discovery and treatment of patients, and in some areas to chemoprophylaxis in addition, the present overall low rate of 0.1% was probably partly the result of a natural recession of the disease. It would be the duty of the Sleeping Sickness Service to detect and combat any recrudescence.

Dr. MICHAEL P. S. HUTCHINSON (West African Institute for Trypanosomiasis Research), after showing a coloured film illustrating the field methods of diagnosis and treatment, discussed the treatment of gambiense trypanosomiasis with melarsen.* From tables compiled from field trials he showed clearly that, while good results followed the treatment of early cases of gambiense trypanosomiasis with combinations of suramin and tryparsamide, intermediate and late cases could be more effectively treated by melarsen. Melarsen oxide and Mel B were too toxic to be used except under close medical supervision, Mel B having a limited field of use in advanced cases only. Melarsen was of special value in combating tryparsamide-resistant strains and in relapses. Probably somewhere between 20 and 30% of the 7,000 cases diagnosed annually in Nigeria, Ghana, Sierra Leone and the Gambia needed more than one standard course of suramin and tryparsamide and might thus be considered suitable for melarsen. A safe dosage rate was one not exceeding 20 mg. per kg. body weight intravenously at five-day intervals for 12 injections. In advanced cases where medical supervision was available 30 mg. per kg. gave considerably better results.

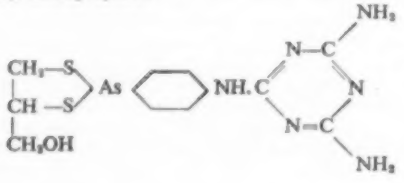
*Melarsen is a pentavalent arsenical, the disodium salt of *p*-[2:4-diamino-1:3:5-triazinyl-6] aminophenyl arsonic acid



This is not to be confused with melarsen oxide, a trivalent arsenical, *p*-[2:4-diamino-1:3:5-triazinyl-6] aminophenyl arsenoxide



Melarsen oxide combined with BAL (dimercaprol) is now known as Mel B. It is *p*-[2:4-diamino-1:3:5-triazinyl-6]-aminophenyl arseno-α-β dithiopropanol.



Mel B in East Africa

Dr. FRANK I. C. APTED (Tanganyika) discussed Mel B in the management of rhodesiense trypanosomiasis. When he had transferred from Sierra Leone to Tanganyika in 1951, the situation facing him was that a patient within a month of infection by *Trypanosoma rhodesiense* usually had his nervous system involved and the trypanosomes themselves were almost invariably resistant to tryparsamide. There was little hope for the patient once obvious changes had appeared in his cerebrospinal fluid. At this time Dr. Apted was given some Mel B for trial. Of the first 33 patients treated about half remained cured, whereas formerly none would have been expected to survive. In a further series of 176 late cases 10% died, 7% relapsed, and the remainder were cured. Of seven cases which relapsed six were cured by further courses of Mel B.

Initial dosage of Mel B should not be based on mg. per kg. body weight, but rather on a clinical assessment of the patient's general condition. The more severely ill required small doses at first and might gain from having suramin beforehand. The full dosage was 3.6 mg. per kg. body weight intravenously—i.e., 5 ml. of the 3.6 w/v solution for a man weighing 50 kg., but the first dose should not be more than 2 ml. and might well be as little as 0.5 ml. Further doses were given on the second and third days, followed by a rest period of one to two weeks and then by a second series. Where the patient's enfeebled condition had necessitated a very small initial dose, further courses might be required over a period of four to five weeks. Additional dimercaprol was useful in combating toxic reactions. With careful dosage toxic reactions were not too serious, considering the patients were otherwise doomed, but the treatment was carried out in hospitals within reach of the sleeping sickness areas. Some cases failed to respond to the drug, apparently owing to a breakdown of the body's defence mechanisms. Those which recovered did so completely, with no mental or physical sequelae. In the rural dispensaries early cases were treated by suramin, later cases being referred to hospital for Mel B. There remained a danger that strains of trypanosomes resistant to melarsen oxide would develop, but other compounds of a different structure were now under investigation.

After a short discussion the meeting terminated with a vote of thanks to the three speakers.

"I have never been a prophet of gloom regarding the failure of Nature's supplies and the imminence of world famine and, thanks to the chemist, we have survived the days when world starvation was thought to be inevitable through the depletion of our natural nitrate supplies, a danger averted by the brilliant researches of Haber and La Rossignol on the fixation of atmospheric nitrogen. Recently the director of the Commonwealth Bureau of Dairy Science and Technology, Mr. A. W. Marsden, expressed the view that whereas the present population is estimated at 2,500 million he believed the world could feed 5,000 million people. He rejected pessimistic views on the subject but considered that a greater application of science to agriculture would be needed."—Sir IAN HEILBRON, F.R.S., in a lecture on "Expanding Horizons in Organic Chemistry," delivered to the Royal Society of Arts on May 14.

To-day's Drugs

Under this heading we hope to publish from time to time authoritative notes on a selection of new drugs.

Ovestin (Organon Laboratories).—These tablets contain 0.25 mg. of oestriol, which, by most criteria, is the least active biologically of the commoner naturally occurring oestrogens. It has been claimed that, when taken by mouth, this hormone exerts oestrogenic action on the vaginal and cervical epithelium without producing endometrial changes and so is recommended for the treatment of post-menopausal vaginal and cervical lesions. These claims are unconfirmed. The hormone has also been recommended for the treatment of so-called functional dysmenorrhoea, one or two tablets being taken daily during the second half of the menstrual cycle. Though treatment of dysmenorrhoea by oestrogens given to suppress ovulation has a rational basis and is usually effective, post-ovulatory oestrogen therapy appears to be empirical, and, in the writer's experience, usually completely ineffective. It is difficult to see how a very weak oestrogen, given in this way, could palliate dysmenorrhoea except by suggestion.

Primolut N (Schering A. G., Berlin, distributed by Pharmethicals, London, Ltd.).—This is a 5 mg. tablet of norethindrone, otherwise known as 19-nor ethisterone (17α-ethinyl-17-hydroxyoestr-4en-3one). Norethindrone is an orally active progestogen, the precise potency of which has not yet been adequately worked out. Claims that it is some ten times as active as ethisterone are almost certainly exaggerated, and in the writer's experience the potency ratio would appear to be nearer five.

It is not generally appreciated how much ethisterone is needed to produce significant progestational effects; not less than 80–100 mg. daily for 10 days is required to produce a secretory endometrium, though withdrawal bleeding from a non-secretory endometrium will take place after a much shorter course at far lower dosage. Nevertheless, in the treatment of threatened and habitual abortion, for which ethisterone is commonly given, the doses most often prescribed, of 10–40 mg. a day, are little more than homœopathic. With norethindrone it should be easy to reach a pharmacologically effective level with, say, 20–30 mg. daily. In view of the enhanced potency of norethindrone, it is appreciably cheaper to use than ethisterone, though still very expensive.

Tessalon (Ciba Laboratories Ltd.).—Tessalon is a new kind of cough suppressor. Whereas codeine and dextromethorphan act centrally, reducing the reflex response to the cough stimulus, tessalon acts by anaesthetizing the dilatation receptors in the lung, preventing the excessive dilatation of the lung which precedes coughing, and interrupting the afferent branches of the reflex arc. Other anaesthetics also suppress coughing in this way, and their chemical analogues were studied to find a substance which had a sufficiently selective action on the lung receptors. Tessalon, which is 2-(ω-methoxyoctaethyleneoxy)ethyl *p*-butylaminobenzoate (benzonatate), is related to amethocaine.

Clinical trials in Switzerland and America have shown that it is at least as effective as codeine, and has no sedative action. It is particularly effective in relieving cough of pleural origin, though it does not relieve pleural pain. It is is also said to be effective in chronic bronchitis and bronchial carcinoma, but less so in acute bronchitis. A 100-mg. capsule given orally acts within 15–20 minutes and is effective for 3–8 hours. Some patients are benefited only after several days' administration, which indicates a cumulative action. Repeated doses have, however, been given for long periods to patients with tuberculosis, without signs of toxicity and with no loss of effectiveness. Side-effects, which include diarrhoea and headache, have been few.

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

Oesophageal Atresia

SIR,—I was most interested in the article on "Oesophageal Atresia" by Mr. Christopher Parish and Mr. C. F. A. Cummins (*Journal*, May 17, p. 1140). I am in agreement with most of the suggestions put forward with regard to diagnosis.[1] Two points I think should be emphasized here. The first is that midwives should be taught about the condition, as they will often be the first to see the suspicious signs; and secondly any child who is noticed to have a congenital abnormality such as an "imperforate anus" should have a catheter passed down the oesophagus. The earliest case in my own series was operated upon when she was 12 hours old, having been diagnosed in these circumstances. The possibility of a tracheo-oesophageal fistula without atresia must be kept in mind if the signs are suspicious although atresia has been excluded. Fistula without atresia may not be so rare as has been hitherto thought, and I agree with the authors that the diagnosis may be difficult. I showed such a case at a recent meeting of the Royal Society of Medicine[2] in which operation was carried out at the age of 3 months.

With regard to the operation, my own preference is for an intercostal incision, and I agree with the authors that a single layer of interrupted fine sutures is the best way of carrying out the anastomosis. The use of a very fine polythene tube passed down to the stomach when the anastomosis has been completed should avoid the necessity for a gastrostomy. The question of early operation is important, although one survivor in my series was operated on 5½ days after birth. Weight, too, is important, but again it is worth giving the smallest infant the chance of an operation; my two smallest survivors weighed 3 lb. 12 oz. (1.7 kg.) and 3 lb. 13 oz. (1.73 kg.) respectively at the time of birth. It is interesting to note that the subsequent progress of these very small survivors has been quite uninterrupted.

In my last 62 cases of oesophageal atresia, only one child was not operated upon. This child was bleeding from the lungs and an attempt was made to correct this before operation, but without success. Of the remaining 61 cases, seven were of type II and no immediate anastomosis was possible. Of the 54 in which a primary anastomosis was carried out, 26 survived. One of those who died was flown from West Africa, and owing to bad weather the flight was delayed and operation was carried out when the child was 8 days old. The oldest survivor is now 11 years of age and, incidentally, was the first successful case reported outside the United States. Of the survivors, four have had the following associated anomalies: one has colobomata, two had an associated "imperforate anus," and another child, who is now 10 years of age, has developed signs of congenital heart disease and deafness. Associated anomalies in the unsuccessful cases have included: tentorial tear, 2; abnormal tracheal fold,[3] 1; persistent left superior vena cava and patent ductus arteriosus, 1; patent ductus arteriosus and horseshoe kidney, 1; sclerema, 3; imperforate anus, 3; and absence of right kidney and ureter, 1. Post-operative stricture formation has not proved a problem in my own series, although one child developed a stricture at the age of 5½ years. This was the child with colobomata and she had presented feeding difficulties before any stricture could be demonstrated.—I am, etc.,

London, W.12. R. H. FRANKLIN.

REFERENCES

[1] Franklin, R. H., *Surgery of the Oesophagus*, 1952. Edward Arnold, London

[2] *Proc. roy. Soc. Med.*, in press.

[3] Franklin, R. H., and Graham, A. J. P., *Thorax*, 1953, **8**, 102.

Diagnosis of Cardiac Infarction

SIR,—One has grown accustomed to the periodic publication of evidence devaluing many of the clinical methods and artifices one grew up with; recently, for example, Rovsing's sign in acute appendicitis has been added. Such evidence, carefully collected often over lengthy periods, carries conviction, and is accepted—albeit with resignation and perhaps the thought that most of our older teachers appeared to practise their unsound techniques with remarkably good results. To be deplored, however, is the trend towards inferential condemnation of established clinical methods, of which an instance is contained in your annotation (*Journal*, April 26, p. 991) on errors in the diagnosis of cardiac infarction. The annotation begins: "The electrocardiograph is an essential tool for the accurate diagnosis of myocardial infarction . . . a wide margin of error may be expected . . . without the aid of a full electrocardiogram." The note concludes: " . . . no clinical diagnosis of myocardial infarction should ever be considered sufficient without the confirmation of an electrocardiogram, however 'classical' the symptoms may appear to be."

The same issue of the *Journal* (p. 1016) contains the weekly exhortation to order the excellent publication deriving from the same source, *Emergencies in General Practice*. At page 59 of this book Dr. A. Morgan Jones writes: " . . . if the electrocardiogram does not show any evidence of recent infarction this should not be regarded as proof of the innocence of the symptoms. . . . In fact, the investigation is useful only when the result is positive, and then its value probably lies as much in the handling of the patient and his relatives as in clarifying the clinical diagnosis." My own experience comes down heavily on the side of Dr. Morgan Jones—patients with suspicious histories and normal E.C.G.s dying in failure not long afterwards, a course of events often predicted by the clinician interpreting symptoms and signs alone. It is not my purpose, however, to stir into activity the advocates of one point of view or the other, but to venture a criticism of dogmatic assertions of opinion on matters which are (*vide supra*) undecided.

The general practitioner, conscious of congestion in consultative clinics and of pressure on specialist domiciliary services, finds himself in some difficulty. Doubtless many rely, as I do, on leaders and annotations in the *Journal* to keep up to date with authoritative opinion. Confronted with this annotation, is he then to carry on as before, accepting clinical evidence at the bedside in very many of his "coronaries"? Or is he in all cases, both clear-cut and doubtful, to have an E.C.G. undertaken? Clearly your annotator favours the latter course. I am happy to raise the point before cardiologists and their staff fall victim in their hundreds to the same disease.—I am, etc.,

Woodley, nr. Stockport. R. L. GOLDSON.

Contaminated Infusions and Transfusions

SIR,—I was particularly interested in the paper by Dr. T. Gilat, Dr. M. Hertz, and Mr. G. Altmann on "Severe Shock Syndrome due to Contaminated Infusions" (*Journal*, May 10, p. 1104), since it helped us to solve a very similar problem.

The patient concerned was a woman aged 47, who was being prepared for hysterectomy which had been advised for prolonged dysfunctional uterine haemorrhage and secondary anaemia (haemoglobin 55%). In the course of receiving the last of three bottles of compatible blood by transfusion, she developed some backache and then a rigor. The transfusion was stopped after approximately 300 ml. (or two-thirds) of the blood in the last bottle had been administered. The shock syndrome was discovered some 24 hours later, when the patient was found gasping in bed. The possibility of a mismatched transfusion was excluded by carefully rechecking the patient's blood group and the blood used for the transfusion. Unfortunately, the blood then remaining in the bottle was discarded before the idea of its being infected first arose.

The shock syndrome in this case was similar in practically all respects to that described by Dr. Gilat and his colleagues, except for the absence of high fever: the temperature never exceeded 99.8° F. (37.7° C.). Restlessness, flushing, and abdominal pain were striking features, but, instead of vomiting, the patient had several bouts of diarrhoea. The laboratory data showed little worthy of note, except for an initially high blood urea and a transiently raised serum bilirubin. The shock was treated with methedrine and cortisone, but the blood pressure did not respond, and the urinary output increased for 24 hours or so.

Two conclusions are drawn from this case: the greater safety of treating pre-operative anaemias with iron in outpatients, and the danger of infecting blood in the process of cross-matching when pilot bottles are not supplied by the blood transfusion centres. I first saw pilot bottles, securely fixed to the main bottles, in use in America eight years ago, when they were filled at the time of venesection. The arguments advanced by some transfusion experts against them become groundless when it is realized that they have been adopted in some regions, apparently without trouble. May I make a strong plea for the introduction of pilot bottles where they are not already available? They would surely go a long way towards avoiding infecting blood and causing this sort of shock syndrome, particularly where cross-matching has to be done in a general pathology laboratory.—I am, etc.,

London, S.E.18. E. G. JONAS.

Conscientious Objection to Transfusion

SIR,—I have read your legal correspondent's note under the above heading in the *Journal* of April 5 (p. 838) with great interest but some reservation. Whilst it may be argued that it is the moral duty of every citizen to prevent the commission of crime if he can, do all doctors feel that it is incumbent on them to inform the police whenever they learn during the course of a consultation with a patient that a crime may shortly be committed? If they do not feel this, is it your legal correspondent's opinion that they are failing in their duty?

Suppose the doctor does inform the police, how would this, in the words of your legal correspondent, "prevent what would have been in the eyes of the law an intentional killing"? The police can have no power to compel parents to permit their child to have a transfusion. Is it suggested that they have power to remove the child from the parents' custody immediately after its birth, and to arrange for a transfusion to be given? Even if they have such power, could it be exercised quickly enough to save the child's life? In the absence of such power does your legal correspondent think that Jehovah's Witnesses are more likely to be amenable to the pressure of the police than they are to the reasonable persuasion of their own doctor?

Is not the most practical solution to give the child a transfusion despite the parents' protests, provided, of course, that the doctor is quite satisfied that such transfusion is necessary to save the child's life? The worst that could happen then is an action for assault, but surely, where the alternative to a transfusion is death, no such action is likely to be successful.—I am, etc.,

London, W.1. J. S. TAPSFIELD,
Legal Adviser,
South-west Metropolitan Regional Hospital Board.

Compulsory Blood Tests

SIR,—Whilst the reasons put forward by the Court of Session against these (*Journal*, April 5, p. 838) are of course to be viewed with respect and would, as your legal correspondent states, almost certainly be followed by an English court, it seems that support can be found, on a purely legal as distinct from scientific basis, for the contrary view. If a person is in possession of evidence that may be material in legal proceedings, he can be subpoenaed to produce such evidence, and can be forced to supply to the court any relevant object—e.g., a document—in his possession. The nature of a person's blood can be material evidence, and it does not seem logical that he should not likewise be compelled to reveal this to the court.—I am, etc.,

Chester. V. BISKE.

Thoracic Actinomycosis

SIR,—With reference to the article by Drs. Ewart M. Jepson, F. Clifford Rose, and Richard D. Tonkin (*Journal*, May 3, p. 1025), I was very interested in the presentation of these two cases, which brought to mind a case I had in 1947.

From memory I recall this female patient presenting with a painful tumour the size of a small apple in the upper half of the left breast, low-grade temperature, mild leucocytosis (14,000), and on *x*-ray examination a mass nearly the size of a football in the left lung field. The history was of 10–14 days' duration. The diagnosis was definitely made when this empyema necessitatis burst through the skin. She was given 1–2 million units of crystalline penicillin daily for, I think, 3–4 weeks and she relapsed again after a short time; this course was then repeated. I suggested that potassium iodide should be given in the hope that fibrous tissue around the periphery of the lesion might be broken down and allow the penicillin to reach the centre of the lesion in greater concentration. This was given with the second course of penicillin and an excellent result obtained. This girl married and had two children, and the last time I heard of her she was still in good health.

I suggest that potassium iodide may be the answer (with penicillin) to obtain the maximum concentration of the antibiotic in the centre of the lesion and thus diminish the number of cases that fail to respond to antibiotics alone.—I am, etc.,

Langley. L. L. MISTLIN.

School Medical Inspections

SIR,—I am in agreement with much of Dr. T. A. Petrie's letter (*Journal*, May 17, p. 1178), but to my mind he omits one point of paramount importance—the co-operation of the teaching staff—and it is only when this triumvirate is obtained that school medical officers are completely successful. He raises another point of great importance—namely, that of continuity, which is only possible after some years of service: one has only to see the satisfaction—dare one say pleasure?—of parents when they meet an officer whom they have known for some time. Is it surprising, though, that many school medical officers are birds of passage when most local authorities are content to pay their officers, no matter what their length of service, the maximum of an inadequate scale our reluctant negotiators have wrung from still more reluctant arbitrators.

It would seem, then, that the School Health Service of the future will be competently staffed only if officers have a love for the work and/or private means. The first condition may or may not persist, the second certainly will not within the state of our economy in the foreseeable future.—I am, etc.,

London, W.8. HELEN E. ORMISTON.

Cost of Treatment

SIR,—Many of your readers must have been alarmed at the implications of the second sentence of your leading article on "Steroids in Treatment of Asthma" (*Journal*, May 17, p. 1166). This states that prednisone and prednisolone are five times more potent than cortisone but *seven times more expensive*, the implication seeming to be that a course of treatment with the delta-steroids costs seven times as much as with cortisone, which is absurd. What may have been meant is that a mg. of prednisone or prednisolone costs seven times as much as a mg. of cortisone. Even this, however, is no longer true. Since May 5 a 5-mg. tablet of prednisone or prednisolone has cost only 1.1 times as much as an equivalent 25-mg. tablet of cortisone (previously the cost ratio was 1.31). When considered in relation to the great advantages of the new steroids over cortisone, the extra 10% cost is small.

Surely when the costs of similar drugs are being compared they should be related to equivalent doses and not to a common measure of weight.—I am, etc.,

London, W.1. OLIVER GARROD.

Polio Vaccination

SIR,—I will be most interested to hear if there have been any reactions to British poliomyelitis vaccine similar to the case which I have encountered in my practice.

The patient is the son of a colleague, his age is 3 years old. Four days after the administration of his first dose of 1 ml. of "polivirin" he became irritable, was off his food, and he had a mild pyrexia up to 101° F. (38.3° C.). He complained of pains in his legs and was disinclined to walk or use the right leg. (The injection was given into the deltoid region of the left arm.) His mother, a keen observer and physiotherapist, thought he looked as if he had suddenly developed a flat foot. His father examined him and thought there was weakness in the extensors of the right leg. The boy started to improve after 72 hours. I visited him on May 14 and could find no abnormal signs.

The assistant medical officer of health, who accompanied me, described a similar case that he had visited. We discussed this case together, and neither of us was able to make a definite diagnosis. Was it coincidence? Had the injection acted as a trigger which fired off non-paralytic poliomyelitis due to an incubating virus? Was this due to the injection of live virus?—I am, etc.,

Preston, Lancs. GEOFFREY H. PIMBLETT.

SIR,—I write with reference to Dr. Michael Carter's letter on "Polio Vaccination" (*Journal*, May 3, p. 1067). At a recent symposium on poliomyelitis at University College Hospital, London, it was stated (with experimental evidence) that the risk of acquiring severe paralytic poliomyelitis was four times greater for those whose tonsils had been removed than for those who still had their tonsils.

Both doctors and lawyers tend to be drawn from upper-income families where before the advent of the National Health Service the children were more often subjected to tonsillectomy than were the children of the nation as a whole. May it not be that part of the increased mortality of polio in doctors and lawyers is due to their lack of tonsils? Could it be argued that the great increase in incidence of poliomyelitis during the last ten years is due to the large numbers of more susceptible people created by the indiscriminate use of tonsillectomy for the past thirty or forty years?—I am, etc.,

Bromley, Kent. JOAN NEWTON.

Tetanus Immunization

SIR,—May I add a word of support to Dr. Thomas L. Scott's plea (*Journal*, May 17, p. 1176) that serum should not be given in casualty departments where evidence is produced that active immunization against tetanus has been carried out?

For many years now at Mill Hill School active immunization has been done systematically and boys so protected are provided with a card to carry in their wallets, which clearly states that they are actively immunized, and which requests that, if any injection should be deemed necessary, toxoid should be given. In spite of the production of this evidence, on more than one occasion recently, serum has been administered in casualty departments. One would have thought that a casualty officer would have been only too pleased to avoid the responsibility of giving serum in such a case, and to give it in such circumstances would seem to be not only reprehensible but might well be held to constitute negligence in case of any untoward effects of the serum.—I am, etc.,

London, N.W.7. A. H. MORLEY.

SIR,—I read with great interest a letter from Dr. Thomas L. Scott (*Journal*, May 17, p. 1176) on the use of toxoid and A.T.S. I think the points he makes should be emphasized up and down the country. I think, however, it should be made clear to Dr. Scott that it is extremely difficult in a busy casualty department for anyone to find out if patients have previously been immunized by means of toxoid. In the nine years since I took charge of this department not a

single patient has ever volunteered that he has been immunized against tetanus. I make a practice of inquiring from ex-Service candidates whether they have knowledge of immunization against tetanus. It is rare to get any satisfactory answer.

I would suggest that, in every case where immunization has been carried out against tetanus, a suitable card should be provided for the patient, on which is stated unequivocally that this has been carried out. The responsibility for providing this should fall (*a*) on welfare clinics where the triple vaccine is used, (*b*) school medical officers, and (*c*) medical officers in the armed Forces.—I am, etc.,

Casualty Department, The General Infirmary, Leeds. MAURICE ELLIS.

Management of Tetanus

SIR,—The letter by Drs. H. A. Reid, D. P. Bowler, and L. T. Scott (*Journal*, March 9, p. 772) is a very pertinent commentary on tetanus treatment and the problems of its assessment. For the bulk of the world's population, for whom full prophylaxis is impracticable in the foreseeable future, this disease is a major medical problem; and its relative importance as an infective disease increases. At the University College Hospital of the West Indies last year it was encountered more frequently than typhoid, malaria, or poliomyelitis.

Too many commentaries in the past have been based on the dubious assumption that an apparent decline in the mortality rate of tetanus is attributable to an increasingly elaborate therapeutic approach. To take but a few examples: In the Mayo Clinic[1] mortality has declined in each decade. The recent survival of 19 out of 26 cases is credited to antibiotics, tracheotomy, and teamwork; senior representatives of 10 different specialties ponder over every case. In the Sudan[2] in 1939 there were 17 survivors out of 22 cases. The material included lion bites and spear-wounds liable to first-aid treatment with cow-dung compresses. The team consisted of locally trained dressers armed with sulphapyridine and bromethol; there was no penicillin and no A.T.S.

Forbes and Auld[3] reported 15 consecutive recoveries with routine tracheotomy and heavy sedation. In the Kingston Public Hospital in a recent 12-month period 22 cases were treated, with two deaths, and there were 15 consecutive recoveries. Treatment in this area is "conservative" in that the patient is nursed in the open ward with a minimum of sedation, surgery is only performed as indicated by the state of the lesion *per se*, and a high fluid and calorie intake is maintained—as far as possible by mouth. Manual artificial respiration is given for apnoea. The prone position advocated by Dr. Reid and his colleagues is an excellent one if the patient acquiesces; children seem to accept it better than adults, but it is poorly tolerated by the important patients with respiratory distress.

Not surprisingly, this treatment fails in many of the severe cases—and, as was pointed out by Dr. Reid and his colleagues, in certain cases not recognizably severe. On this régime a mortality of 29% occurred in 100 recent cases. This figure, admittedly of limited significance, serves as a reminder of what must be achieved in order to establish that any other measures are of benefit—observations of which are in hand.

The most readily detectable influence of hospital treatment is in fact liable to be an adverse one associated with oversedation, the side-effects of drugs, or the various complications of mechanical interference with respiration. Thus Lassen *et al.*,[4] in describing the long-term positive-pressure treatment of tetanus, mentioned that in one surviving case, in addition to other complications, collapse of the lung had occurred eight times. There must be few centres in the "tetanus area" of the tropics where such trivia can be handled with such aplomb.

With regard to spasms, Dr. William A. Hanna stated (*Journal*, February 22, p. 460), "If spasms cannot be controlled the outlook is serious." This is a widely held view, but I feel it is more apposite to say that if the outlook is serious the spasms may be difficult to control. Mortality does not directly depend on spasms, and the pathology and mode of death (which are the subject of special study here) are not such as to lead one to expect benefit from measures aimed purely at a depression of nervous excitation. Creech *et al.*[5] have drawn on enormous experience; yet their conclusion that respiratory infection is the major lethal factor is another widely held view which I cannot correlate with our own findings. We have, however, been impressed by the overwhelming significance of central cardio-respiratory failure.

Untreated tetanus is a self-limiting disease in a few weeks, however "chronic" the source. Yet it is not an immunizing disease as judged by antibody response to the exotoxin which occurs *in vitro*. These two facts provide food for deep thought.—I am, etc.,

Mona, Jamaica. R. D. MONTGOMERY.

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Trench-foot

SIR,—I was interested to read the paper by Dr. R. C. King, Dr. J. A. Parrish, and Dr. A. Allibone (*Journal*, May 10, p. 1099) describing three cases of trench-foot which had occurred recently in this country. I was reminded of a similar case which I was able to see whilst serving in one of our Royal Naval Hospitals in 1956.

In the spring of that year a National Service infantryman was admitted to this hospital having gone absent without leave eight days previously. He slept outdoors every evening in particularly cold weather, and throughout his "leave" had worn his heavy Army boots.

On examination he was himself well, but his feet were very swollen, cold, and mottled with cyanosis over the proximal parts, whilst the toes were white and there was full-thickness skin blistering over the dorsum of the great and first two smaller toes on each side. Peripheral pulsation was vigorous. He was treated with bed rest; the feet were caged and left open to the air; he was given prophylactic penicillin and tolazoline 25 mg. four-hourly by mouth, but anticoagulants were not considered necessary. On this he had a very florid peripheral vasodilatation, and gradually over the following weeks the condition of the feet improved. Unlike the cases described in the *Journal*, this boy did not require grafting, for the lesions granulated slowly but completely.

I feel certain that many accounts of similar cases are to be found in the records of Service hospitals throughout this and other countries.—I am, etc.,

Newcastle upon Tyne, 1. J. B. FOSTER.

SIR,—I was very interested in the article on "Trench-foot in Peacetime England" by Drs. R. C. King, J. A. Parrish, and A. Allibone (*Journal*, May 10, p. 1099), as recently I have had under my care a comparable case.

This was a man of 27 years of age who was working in Sheffield. He disappeared from his lodgings at the beginning of March of this year and was found by the police ten days later. Mentally at that time he was very confused and had little recollection of where he had spent the previous ten days. He was brought by his father to his home in Ireland and was admitted to hospital on March 21. At that time he had gangrene of all the toes of the left foot, with oedema spreading up above his left ankle. On the right foot there was patchy gangrene of the tips of the great toe and the little toe with a less severe degree of oedema extending to the ankle. No abnormality of renal function or of the cardiovascular system was found and the pulsations in the major arteries of both legs were normal.

He was treated by exposure of the affected parts to room temperature and antibiotics. The oedema slowly subsided and the line of demarcation of the gangrenous area became more definite. It was only at this stage that he complained of any pain. A forefoot amputation was carried out on the left side on April 17, with healing of the wound by first intention. The small superficial gangrenous areas on the toes of the right foot were allowed to separate and have now healed.

—I am, etc.,

Rostrevor, Co. Down. G. W. VAUSE GREIG.

Out-patient Gynaecology

SIR,—We were delighted to read in Mr. Albert Davis's letter (*Journal*, May 17, p. 1177) that vaginal smears were finding their way into gynaecological out-patients, though we gather as yet their intrusion is only appreciated by the "scientifically minded gynaecologist." Apart from the early diagnosis of uterine cancer, surely they are the simplest and quickest way of assessing ovarian function, and therefore can be useful in the diagnosis and treatment of many gynaecological and endocrine disorders—e.g., primary and secondary amenorrhoea, repeated miscarriages, the menopause, etc.

As the majority of patients can be instructed to take their own vaginal smears it is possible to obtain a continued rather than an isolated study of their ovarian activity without admission to hospital, and it therefore seems a pity that this diagnostic aid is not more widely used in this country.—We are, etc.,

FREDA OSMOND-CLARKE.
MOIRA MURRAY.

London, S.W.3.

SIR,—Mr. Albert Davis in his letter on this subject (*Journal*, May 17, p. 1177) shows clearly that he is a hospital doctor and not a general practitioner. If he were the latter he would know (1) that patients often tell surgeons that they are "cured" (Mr. Davis's own word) in order to escape a further ordeal in hospital; (2) that patients often tell physiotherapists that they are "relieved" (Mr. Davis's own word) because they would rather put up with the pain of backache than submit to the ministrations of a physiotherapist for longer. Massage and application of local heat—the only things a physiotherapist can accomplish for them—are calculated to produce more pain than almost anything I can imagine.

Mr. Davis is completely wrong when he suggests that "the majority of these troubles . . . react so well to purely physical treatment." They do not. The general practitioner has to cope with these patients for years, going on and on making the same complaints for which physical treatment was given in hospital. Clearly we who undertake the whole care of the patient for the whole of her life are in a better position to be able to judge the effects of treatment. I for one remember no patient who benefited from orthodox physical treatment for any of the disorders mentioned originally by Drs. Norman Morris and Desmond O'Neill (*Journal*, May 3, p. 1038).—I am, etc.,

London, S.E.5. JOHN HENDRIE.

Chemotherapy in Primary Pulmonary Tuberculosis

SIR,—We are grateful to Dr. R. Munro Ford (*Journal*, April 12, p. 887) for drawing attention to our failure adequately to discuss our conclusions concerning the value of antibiotics in the patients in our series.[1] We take it that by the term antibiotic therapy is meant the systematic use of combinations of the three drugs, isoniazid, P.A.S., and streptomycin. The assessment of such therapy in primary tuberculosis was not, however, the purpose of our paper; nor would it have been possible from the available data, for, as we stated, patients were treated with or without antibiotics by the doctor in charge of the case for varying lengths of time before coming under our care in hospital, and whether or not antibiotics were administered may have depended on many factors, including the doctor's assessment of the severity of the case when first seen.

Nevertheless, a review of our cases did, if anything, tend to confirm the findings of previous workers[2 3 4] that the *routine* use of antibiotics in all children over 2 years of age with primary tuberculosis was not followed by a more satisfactory final result than in those not so treated. We would, of course, subscribe to the view that antibiotics should be given to all infants with a primary lesion, a practice which has been adopted in our series by the doctors who referred such patients to us, for, as we pointed out, all children under 2 years of age had received antibiotics from the outset, and this therapy was continued in hospital. The fact that the only fatalities in this series, both from meningitis, were in babies so treated emphasizes the dangers of complications in the very young and therefore the advisability of early antibiotic therapy, though it cannot be said to confirm its efficacy.

Whether antibiotics from the outset in all our patients would have reduced the incidence of permanent lung damage or other complications, as suggested by Dr. Munro Ford, must be uncertain. However, in most patients with segmental pulmonary lesions, the lesions were established at the time the diagnosis was made, and in those treated in hospital from the beginning without antibiotics the incidence of permanent lung damage was not greater than in those treated with antibiotics. Moreover, we could demonstrate no difference in the rate of resolution of the lung lesions in the groups. Similarly, the development of adult-type pulmonary lesions and the incidence of skeletal complications or of meningitis was no less in those receiving antibiotics from the outset than in those not so treated. Nevertheless, we did not consider that our data justified any firm conclusions on the value of antibiotics in the prevention of these complications, and we should have made it clear that, in concluding that "additional use of antibiotics does not seem to offer any advantage" in treatment, we were referring only to the results of our observations on the course of the condition in our patients while under our observation, which in no case exceeded 8 years.

Dr. Munro Ford discusses the value of antibiotic therapy at length in his letter without any reference to the possible development of drug-resistant tubercle bacilli or the part which the patient's own resistance may play in combating the disease—surely of some importance? Moreover, if antibiotics are to be used prophylactically, where shall we draw the line? Is every child who converts a Mantoux reaction to be so treated? It is not without significance that the issue of the *Journal* in which Dr. Munro Ford's letter appeared also carried a leading article (p. 880) on "Neurotoxic Effects of Isoniazid," and, as we all know, deafness following prolonged treatment with streptomycin is by no means so rare as to be ignored—We are, etc.,

J. K. CAMERON.
J. D. HAY.
L. J. TEMPLE.

Wirral, Cheshire.

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Lymphoedema

SIR,—I have read the paper by Mr. G. W. Taylor, Professor J. B. Kinmonth, and Dr. W. G. Dangerfield on "Protein Content of Oedema Fluid in Lymphoedema" (*Journal*, May 17, p. 1159) with interest. The problem of elucidating the pathological processes responsible for the production of the clinical picture of lymphoedema is a tantalizing one and offers an increasingly great challenge to surgeons and biochemists. An analysis of the oedema fluid is a very necessary step towards the solution of this problem, but suitable methods are hard to find.

It would be of interest to know how these authors have overcome the difficulty of using the biuret method to measure the total protein concentration in tissue fluid, since in my experience fluid obtained from the subcutaneous tissues of the legs in patients suffering from the condition has a high fat content. I was not able to extract fat sufficiently well to yield a clear solution, and I found that any turbidity interfered with measuring the colour density of the biuret reaction. When I determined the protein concentration by the microkjeldahl method I obtained results which were much higher, the average being 5.5 g. protein per 100 ml. tissue fluid, which confirmed my impression of the unreliability of the biuret method in these particular circumstances.

Electrophoretograms are of great interest in this condition, but here again I found it was not possible to calculate the albumin/globulin ratio, as I repeated the work of Crook *et al.*[1] and was thereby convinced that the light absorption of dyed proteins in an immersed filter paper did not obey Beer's law. Franglen and Martin[2] also showed that the characteristics of the relation of dye-binding to protein concentration differ from one protein to another, and that, if two protein solutions of known concentration are mixed in predetermined proportions and are then separated by electrophoresis, the proportions of these components calculated by dye-binding techniques fail to tally with the predetermined ratio.

It is difficult to accept the statement that "capillary permeability is unaltered in uncomplicated cases of lymphoedema." The physiology of the capillary wall depends on the structure of the vessel wall and the physical laws related to it. Capillaries are certainly not inert, thin-walled tubes, conducting blood through the tissues in whatever quantity the arterioles might supply, and any measurement of capillary permeability must be based on a comprehension of these facts. It is doubtful whether a quantitative analysis of the protein concentrations of extravascular interstitial fluid casts any light at all on the permeability of the capillaries. Certainly the capillary pressure and colloid osmotic pressure are opposite in sign but have the same order of magnitude; but the rate of flow through the capillary membrane is proportional to pressure gradient, tissue pressure modifying the movement of fluid through the capillary wall and normally preventing excessive filtration. Since flow through a macroscopic laminar flow system is inversely proportional to the viscosity of the fluid contained within it, this law probably applies to capillary permeability also. Hence it is doubtful whether conclusions on the state of capillary permeability in lymphoedema can be made without controlling these physical factors, and in addition a histological study of the architecture of the capillary wall and its three structural components should be undertaken before arriving at any such conclusions.—I am, etc.,

Manchester, 13. D. A. BIRCH.

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Chlorothiazide

SIR,—The potentiating effect of chlorothiazide on ganglion-blocking drugs in many patients under treatment for hypertension is well established (*Journal*, April 26, p. 990), but the extent and abruptness of this action are probably not fully appreciated. When the existing dose of a ganglion-blocking drug is failing to produce a satisfactory fall in blood pressure the addition of chlorothiazide may result in a sudden drop to hypotensive levels with accompanying faintness and dizziness or actual syncope. These risks are obviously greater where patients cannot be kept under close supervision, but exist even when they are being seen at frequent intervals.

Early in our experience with chlorothiazide as an adjuvant to the treatment of hypertension, six patients showed the effects to which reference is made, and the details are given in the Table. One patient actually lost consciousness whilst telephoning her doctor to say how ill she felt since beginning the combined treatment.

Case No.	Ganglion-blocking Drug	Blood Pressure (mm. Hg) Before Chlorothiazide		Chlorothiazide Added (g.)	Resultant Blood Pressure (mm. Hg)		Effect
		Lying	Standing		Lying	Standing	
1	Mecamylamine	220/150	170/120	0·5 twice daily	200/140	110/80	Mild faintness
2	,,	230/120	170/105	0·5 twice daily	110/90	—	Faintness and dizziness
3	,,	225/120	—	0·5 three times daily	95/70	—	Syncope; ileus
4	,,	210/125	170/115	0·5 twice daily	170/110	90/70	Faintness and dizziness
5	Pentolinium	260/135	200/145	0·5 twice daily	180/120	130/95	,,
6	Chlorisondamine	185/130	170/120	0·5 once daily	115/75	—	Syncope

Clearly the addition of chlorothiazide should be accompanied by a reduction in the dose of the ganglion-blocking drug and all patients kept under close observation.—We are, etc.,

A. H. KITCHIN.
C. P. LOWTHER.
Edinburgh. R. W. D. TURNER.

Refractoriness to Intrinsic Factor

SIR,—Since the publication of our article describing a patient with pernicious anaemia who was refractory to potent animal intrinsic factor (*Journal*, February 8, p. 322), we have tested the patient's ability to absorb oral radioactive vitamin B_{12} when mixed with larger doses of animal intrinsic factor. We had shown previously that the patient absorbed the test dose of radioactive vitamin B_{12} normally when mixed with 100 ml. human gastric juice, but failed to absorb with doses up to 200 mg. intrinsic factor concentrate (Lederle, Batch 186-1) or 5 mg. purified intrinsic factor (Lederle). Both these experimental preparations in doses of 50 mg. and 5 mg. respectively are adequate to promote absorption of radioactive vitamin B_{12} in the usual patient with pernicious anaemia.

When the radioactive vitamin B_{12} was given with 500 mg. (Batch 186-1), the 48-hour urinary excretion of radioactivity was 14.7%; when given with 100 mg. purified intrinsic factor, the value was 18.5%. Therefore large doses of intrinsic factor are able to effect vitamin-B_{12} absorption in this patient, indicating either that refractoriness to animal intrinsic factor is a relative rather than an absolute phenomenon, or that a different mechanism of absorption is involved when these large doses are used.—We are, etc.,

J. B. STOKES.
Perth, Western Australia. W. R. PITNEY.

Tuberculous Pleural Effusion

SIR,—It seems that in discussions on the treatment of primary tuberculous pleural effusions the pathological basis of such effusions is left out of account. Thus Dr. Arnold Pines (*Journal*, May 10, p. 1120) says that presumably the total population of bacilli is not very large. Yet it has been known for years that in this disease both the visceral and parietal pleura are densely studded with histological tubercles,[1–3] and the success of blind needle biopsy of the pleura in diagnosing tuberculous pleurisy rests on this fact.[4 5]

I would agree with Dr. Pines that the organisms are readily accessible to the drugs. In view of the amount of tissue involved by tuberculous granulations, however, it will be interesting to see whether twelve months' chemotherapy is sufficient, or whether the eighteen months to two years' course now thought necessary in pulmonary tuberculosis will not also be needed for tuberculous pleural effusions.—I am, etc.,

Wroughton, Wilts. PAUL MESTITZ.

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Cancer Education

SIR,—There can be very few members of the medical profession, and there is no evidence of any lay people, who still believe that cancer education increases fear. The problem therefore is how can such education be carried out at practically no expense. It is obvious that family doctors have no time to give lectures, indeed they cannot even spend time in discussing cancer, when they have a crowded surgery. It can only be carried out by the local health authorities through their health visitors, nurses, and midwives. In addition to this, if the Canadian "Little Red Door" service is adopted, it would prove to be invaluable. This service is a cancer information service, an office being set up in most of the towns and villages in Canada, but in the sparsely populated areas a motor caravan is used. It derives its name from the fact that the door of the office is painted red. It is generally staffed by a retired nurse who is willing to do the work for a small honorarium or voluntarily. She does not, of course, examine the patient or attempt to make a diagnosis, but will simply

answer questions and give advice. In many cases it will end by advising the person to go to their doctor, but on other occasions reassurance will be all that is needed and may save the doctors a lot of valuable time. Pamphlets might be sold at cost price, but never more than 6d.

Cancer education will probably save only a few thousand lives each year, but it will enable countless thousands of people to live free from fear of the disease.—I am, etc.,

Oxford. MALCOLM DONALDSON.

Dirty Habits

SIR,—The case quoted by your correspondent, Mr. J. K. Stuart Bell (*Journal*, May 10, p. 1120), appears to constitute a contravention of the Food Hygiene Regulations, 1955. Regulation 14 requires that (1) every sanitary convenience situated in or upon any food premises (*a*) shall be kept clean and in efficient order, (*b*) shall be so placed that no offensive odours therefrom can penetrate into any food room. The onus is clearly on the owner of the food business in question to effect improvements, quite irrespective of whether his customers have dirty habits or not.

If the public were aware of some of the more important sections of the Food Hygiene Regulations and prepared to bring contraventions to the notice of the appropriate local authority, I feel certain that there would be a noticeable improvement in the standard of hygiene, at least as far as the handling of food is concerned.—I am, etc.,

Ruislip, Middx. M. R. CANDY.

SIR,—I read with interest Dr. Jno. Crawford's letter (*Journal*, April 19, p. 943) and I am resolved never to eat nuts in a cocktail bar again.

When trying to educate a patient to improve his hygienic habits I always feel it is just as necessary to impress upon him the need to scrub his nails as to wash his hands, for I believe that the one without the other is a job half done and that, in the case of the general public at any rate, this needs emphasis. It is a common and rather nauseating experience when examining a patient's anal region to find it smeared with faeces, and at such examinations I cannot help noting the faecal-stained underpants of the male. After defaecation the anus should be washed with soap and water as well as the hands.—I am, etc.,

Slough, Bucks. C. G. BROWN.

SIR,—I cannot see much point in this fuss about washing the hands after defaecation. By the time the mere male has arranged his clothing, pulled the plug, opened the door, and turned on the taps in another room he has already done all the dirt and disease spreading needed. Now if cisterns flushed by a foot pedal, and hands could be washed *before* arranging the clothing, and the towels were always sterile or at least clean and unused, there would be some point in it.

The ladies, with much less arranging, are usually better supplied with washing facilities, but the modern "separate W.C." is, sanitarily, ridiculous.—I am, etc.,

Cromer. A. H. GREGSON.

SIR,—When will British plumbers discover that excellent and comfortable device, the bidet ?—I am, etc.,

Burnham, Bucks. AGNES THOMPSON.

*** This correspondence is now closed.—ED., *B.M.J.*

Rheumatology as a Whole-time Specialty

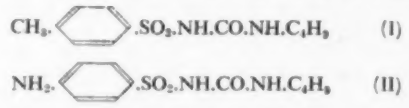
SIR,—Dr. William Tegner and the North-east Metropolitan Regional Hospital Board (*Journal*, May 17, p. 1182) are to be congratulated upon the establishment of a central rheumatism centre and associated peripheral clinics on the lines suggested in the report of the Royal College of Physicians, to which he refers. This is a progressive move which it is to be hoped will be followed by other regional boards and boards of governors. I have no doubt, however, that he will agree that this is only a beginning, and that most parts of the country are badly served so far as sufferers with the more serious rheumatic diseases are concerned.—I am, etc.,

London, W.1. W. S. C. COPEMAN.

Sulphonamides and Sulphanilamides

SIR,—A terminological error seems to be creeping into medical and pharmaceutical literature.

The antidiabetic tolbutamide (I) has been described at least twice as being "not a sulphonamide"—in a leading article in the *Journal* last year (August 10, 1957, p. 343) and more recently in the *Extra Pharmacopoeia* (24th edition,



Volume 1, p. 790). Actually, both tolbutamide and carbutamide (II) are true sulphonamides, but only the latter is a sulphanilamide derivative. Clearly the above description should be amended accordingly.—I am, etc.,

Beckenham, Kent. E. WALTON.

British Qualifications Abroad

SIR,—Dr. I. M. Griffith (*Journal*, May 10, p. 1124) is surely confusing standards with labels.

The L.S.A. and Conjoint diplomas represent standards set by professional bodies, and maintained at a uniform level by boards of independent and senior examiners chosen from many teaching centres. An M.B. or an M.D. is a label only, bearing the stamp of one university. It is an honour, but the standard it represents may vary from the sublime to the ridiculous according to the university, the year of graduation, the personality of the examiners, and the current policy of the senate, most of whose members are not medical.—I am, etc.,

London, W.1. HENEAGE OGILVIE.

SIR,—Dr. I. M. Griffith in his letter to the *Journal* of May 10 (p. 1124) states that in both the United States and Canada the qualifying examination is the M.D. Dr. Griffith himself is shown in the front page of the *Journal* as an L.M.C.C. I understand from a doctor friend who emigrated to Canada a short time ago, himself an M.R.C.S., L.R.C.P., that he recently qualified for practice anywhere in Canada or the U.S.A. by taking the L.M.C.C. How is this to be reconciled with Dr. Griffith's statement and the fact that he himself is an L.M.C.C. ?—I am, etc.,

London, S.W.19. B. J. BOUCHÉ.

Lecture Fees in America

SIR,—During a recent visit two of my colleagues in San Francisco drew my attention to the fact that they were surprised to receive a letter-advertisement which offered to send a visitor from Great Britain to lecture in their departments. This impertinence was capped by the information that a fee of so many hundred dollars would be expected. I have written privately to Dr. X, who was the victim, who replied, of course, that he had no idea that such advertising methods were being used; he naturally undertook to write an explanation and apology which I am sure would be accepted.

One of my colleagues in Birmingham has actually been accosted by advertising agents on the ship at New York. The agent was very plausible, but of course no mention was made of advertising methods which might well cause offence or at least a raising of eyebrows among clinical colleagues in U.S.A.—I am, etc.,

Birmingham, 15. H. C. MCLAREN.

Obituary

R. B. JACKSON, O.B.E., M.D., D.P.H.

Dr. R. B. Jackson, who, as a member of the Colonial Medical Service, had served for many years in Malaya and Hong Kong, died at his home at Bangor, Co. Down, on April 22. He was 79 years of age.

Robert Best Jackson was born at Loughgall, Co. Armagh, on January 4, 1879, and was educated at Dundath Grammar School and Trinity College, Dublin, where he was a mathematical scholar and gold medallist. Graduating M.B., B.Ch. in 1906, he went out to India as medical officer to tea gardens in Assam and then took up an appointment as medical officer with the Indian Mining Association at Jheria and Katrasgarh, in the former state of Bihar and Orissa. Later he became principal medical officer to the company. During a severe outbreak of cholera in the Jheria coalfields in 1913 he won very high praise for his splendid work among the local population. Returning to the United Kingdom soon after the outbreak of the first world war in 1914, he served as a captain in the R.A.M.C., and was for a time resident medical officer at the Edmonton General Military Hospital. He obtained the certificate of the London School of Tropical Medicine in 1914, and another certificate, with distinction, in 1926. He took the Dublin D.P.H. in 1917, and proceeded to the M.D. in 1926. After nearly twenty years of fruitful work in Malaya and Hong Kong he retired from the Colonial Medical Service in 1939, the year after his appointment as O.B.E. During his retirement he worked for a time as medical officer in the Northern Ireland Ministry of Health and Local Government. He is survived by his son, Dr. A. R. B. Jackson, who practises at Abingdon.

A. R. W. writes: In 1921 Dr. R. B. Jackson joined the Government Medical Service of the Federated Malay States, and his first appointment was that of health officer to the State of Negri Sembilan. He soon interested himself in the study of mosquitoes, recognizing this as the first step in the investigation and prevention of malaria, the chief cause of ill-health in that area. He gave valuable assistance in the antimalarial work carried out at Gemas, help which turned that fever-stricken railway junction into a sort of health resort. But his interests were not confined to the anophelines; the culicines he regarded as a menace to comfort which ought to be eliminated, and in a number of cases he was able to ameliorate local conditions, first by identifying the mosquitoes found in houses, then by finding their breeding-places—sometimes considerable distances away—and finally by putting a stop to propagation. In 1930 he was transferred to Hong Kong to become the colony's first malariologist. There he established the Malaria Bureau for the investigation of that disease. The bureau was also used as a teaching centre for dressers, sanitary inspectors, and others interested in the subject. By methodical work and close attention to detail he showed that the anophelines carrying malaria were not *A. maculatus*, as had previously been believed, but *A. minimus* and *A. jeyporiensis*. By precipitation tests he found that *A. maculatus*, which were plentiful in the colony, fed on cattle and pigs and avoided humans. During the construction of the Shing Mun dam—in an area long known to be malarious—the labour force of 2,000, living in non-mosquito-proof huts, never had more than 3% of its numbers absent from work through sickness. Much of the credit for this was due to Jackson and his staff. He freed the European residential area of the Peak from the plague of mosquitoes (culicines) which up to that time had so annoyed residents, for he traced the mosquitoes to their source, a small stream half-way down the mountain, and treated it with oil. By destroying the breeding-places of the mosquitoes, which laid their eggs in the many pools of brackish water near the shore, he made seaside resorts much more agreeable to live in. In 1934 he was selected as one of the Hong Kong delegates to the meeting in China of the Far Eastern Association of Tropical Medicine, before which he read a paper on mosquitoes and malaria. After his retirement he was selected by the Colonial Office to go to Southern Rhodesia to investigate the causes of malaria and to report on the measures which should be taken to deal with it. He returned to Hong Kong for a year after the second world war had ended in order to assist in the re-establishment of the Malaria Bureau pending the return to office of those who had been interned by the Japanese.

Sir SELWYN SELWYN-CLARKE writes: I am glad to have an opportunity of adding a few words to the obituary notice of my old friend Robert Best Jackson. After outstanding contributions to malarial research and control in Malaya, he came to Hong Kong, and until he retired shortly before the Pacific War he was responsible for organizing and for directing the work of the Malaria Bureau in that colony, having a very efficient and hard-working second-in-command in Dr. J. B. Mackie, who succeeded him as Government malariologist. It was always a delight to go out on field inspections of potential anopheline-breeding sites with Jackson, listening to his description—in his warm, rich, Irish brogue—of how he was tackling the problem. He certainly deserved well of all sections of the community, for, until the Japanese attack on Hong Kong, malaria had been banished from most of the island and from parts of the mainland—be it remembered that this was before the discovery of D.D.T., gammexane, and the later more effective insecticides. With all his geniality and good humour, Jackson required (and obtained) keen and intelligent work from his staff, whether from the United Kingdom or Chinese, Indian, Malayan, or Eurasian. His relations with malaria officers in the Services, by whom he was looked upon as the authority in antimalarial control, were always of the friendliest, with mutual advantage to all concerned. The honour he received from King George VI was certainly more than well earned, and the official announcement was universally well received in Hong Kong, in Malaya, where he had left many good friends, and in Ireland.

J. FORBES WEBSTER, F.R.F.P.S., F.D.S. Hon.H.D.D.

Mr. J. Forbes Webster, who was dean of the Glasgow Dental Hospital and School for over 20 years, died on May 5. He was 79 years of age.

John Forbes Webster was born on February 23, 1879. He passed the final examination for the L.D.S. of the Royal Faculty of Physicians and Surgeons of Glasgow in 1901, and for the Scottish triple medical qualification in 1903. In 1915 he became a Fellow of the Royal Faculty of Physicians and Surgeons of Glasgow, and subsequently served several terms of office on its council, besides being an examiner for the diplomas of L.D.S. and H.D.D. (Higher Dental Diploma). The Faculty conferred on him the honorary H.D.D. in 1935, and in 1951 the Royal College of Surgeons of Edinburgh granted him a Fellowship in Dental Surgery, without examination.

J. M. C. writes: The ranks of Scottish dentists have been markedly depleted by the passing of John Forbes Webster. His wisdom and friendship will be missed by many. Forbes Webster's outstanding work was undoubtedly in connexion with the Glasgow Dental Hospital and School. He joined its staff in 1902, and in 1925 was appointed dean in a part-time capacity. Owing to his impetus and organizing ability, it was decided to build and equip an entirely new dental hospital and school at 211, Renfrew Street, to replace the very inadequate existing one. Four years later he became full-time dean. He was due to retire in 1944, but because of the second world war he was persuaded to remain in office until 1947, by which time he had concluded negotiations for the dental school to become part of the faculty of medicine of Glasgow University. During his long association with the

Glasgow Dental Hospital and School he was a lecturer in dental bacteriology and dental surgery and pathology, and an able and skilful dental operator, particularly as an oral surgeon. He was consistently fair and helpful to all, and ever unassuming as an administrator. He would never tolerate inferior work, his principle being quality before quantity, and he possessed an uncanny faculty for detecting superficial knowledge masquerading as profound. A man of integrity, he not unnaturally expected the same from others —this may have been responsible for a very occasional suggestion of brusqueness. It is a fitting tribute to his signal services that a Dean Webster Prize was founded and is now awarded annually to the most distinguished Glasgow graduate in dentistry. He was a founder-member of the Glasgow Odontological Society, inaugurated in 1902 with the object of furthering in the West of Scotland the cause of scientific dentistry, and thereby acting as a barrier to its developing into a mere technical craft. As a personal tribute I should like to add that twenty-two years ago I acquired and absorbed Forbes Webster's private practice into my own. In all negotiations and talks about patients I always found him intrinsically honest and helpful. It is sometimes remarked that when a practitioner takes over another's practice friendship ceases. This was certainly not so with Forbes Webster and myself. In fact I learned to know and appreciate him better than ever before, and in consequence to accept him as a friend in the most exalted sense of the word.

SYDNEY ATKIN, M.B., B.Chir.

Dr. Sydney Atkin, who was a general practitioner in Sheffield and formerly honorary physician to the Sheffield Children's Hospital, died at his home in Sheffield on May 9. He was 69 years of age.

Charles Sydney Atkin was born at Sheffield on February 26, 1889, and was educated at Marlborough and at Gonville and Caius College, Cambridge, receiving his clinical training at St. Bartholomew's Hospital. He qualified M.R.C.S., L.R.C.P. in 1913, and then held the appointments of house-physician at St. Bartholomew's and house-surgeon at the Sheffield Children's Hospital and at the Royal Northern Hospital, London. When war was declared on August 4, 1914, he immediately volunteered and was gazetted a captain in the R.A.M.C., going to France with the British Expeditionary Force. After demobilization he settled in practice at Sheffield, and, in spite of his busy life, he obtained the degrees of M.B., B.Chir. in 1922.

E. F. writes: The medical fraternity of Sheffield has lost a well-known member by the death of Sydney Atkin. He was the fourth of a dynasty of doctors who had practised in Sheffield for more than a century. His great-grandfather, grandfather, and father were all well-known practitioners, the last being a consultant surgeon on the honorary staff of the Royal Infirmary for more than twenty years. He himself for some years was a consultant physician on the staff of the Children's Hospital. The family tradition is being maintained by his elder son. With such a record it is no wonder that Sydney Atkin was not only a valued medical adviser to those members of the community who were his patients, but, though seeking no public office in the city, yet was one whose name was always respected and inextricably part of the professional, social, and athletic life in the district. The quiet, tactful, modest influence he exerted in many spheres was perhaps not fully realized until it was removed, and he himself would have been the first to deny that he had had any such influence. Sydney Atkin's whole character and outlook upon life typified the ideals symbolized by the gates of his College—namely, the one of Humility and the other of Virtue and Wisdom, erected by John Caius when he refounded Gonville Hall, and the third being that of Honour, erected later as a memorial to the founder.

Sydney Atkin was a fine athlete, having in a very marked degree what has been called "the timing instinct" for ball games. He played hockey for Cambridge (1909–10) and for England (1910) against Wales, Scotland, and France. He took part in the Olympic Games in 1920, and in 1921 played for England against Ireland as right full-back when he was 32 years of age. This was a memorable game. The average age of the Irish side was 24 years, that of the English 31, but the latter won 5–3: *experientia docet*. He also was a good tennis player, a keen shot, a good fisherman, and never so happy as when working in his beautiful garden. Some of the contents of the letters he wrote to his parents from France during the first world war were published in the *Sheffield Daily Telegraph*; they illustrated well the ineptitude of war. He practised his vocation in the tradition of his family, and his professional life epitomized his ideal of service rather than self. He must have brought care, sympathy, and encouragement to many. In his latter years he devoted much time to the difficult work of medical boards for the assessment of disabilities, first as a member and later as chairman. It was in this work that his tactful, sympathetic understanding and appreciation of the troubles of others were so conspicuous and made each recipient feel he had been fairly treated. A few months ago his health became precarious, but he accepted his disability with a philosophy so typical of the man. He will be sorely missed by many, and those who have had the privilege of his professional care, and the friendship and hospitality of himself and his wife, will be grateful for having known him. He leaves a widow, two sons, and a daughter, to whom we extend our sincerest sympathy.

Medico-Legal

CONSEQUENCES OF CEREBRAL ANOXIA

[FROM AN EXPERT IN FORENSIC MEDICINE]

On February 25 a man of 27, whose mentality was said to have been reduced to that of a child of 5 after he had been rescued unconscious from a well, was awarded £13,500 and costs in the High Court (*The Times*, February 26). The plaintiff was one of four men who had gone down this well, 28 ft. (8.5 m.) deep, to attend to a petrol pump. The first man down was killed and the others were variously affected by the fumes.

On the same day at Devon Quarter Sessions a schoolteacher of 60 was placed on probation for three years, after having pleaded guilty to the fraudulent conversion of £152 19s. 8d. belonging to a British Legion club (*Western Morning News*, February 26). In mitigation it was stated that his brain had been damaged as a result of a period of oxygen lack, and that he had been a different man since a serious illness and an operation two years previously. This view was put forward by a psychiatrist and supported by the defendant's wife and to a certain extent by the investigating police officer.

Comment

The pathological changes in the brain of patients who have survived anoxia or exposure to carbon-monoxide poisoning in acute but non-lethal circumstances are indistinguishable from each other. The lesions take the form of areas of necrosis, particularly amongst the basal nuclei, where they are characterized by their symmetry. Widespread degeneration of the Purkinje cells often follows anoxia due to anaesthesia.[1]

Anoxic poisons, which include carbon monoxide, cyanide, carbon disulphide, barbiturates, and anaesthetic agents such as ether and nitrous oxide, show a tendency to attack certain sites in the brain, notably the cerebral cortex and the basal ganglia (particularly the globus pallidus). The Purkinje cells of the cerebellum, the Sommer sector, and the cerebral white matter appear to be peculiarly sensitive.[2] The same authors state that patients resuscitated from suicidal hanging (in which carbon-dioxide retention is added to anoxia) may

sometimes survive for days or weeks but suffer from choreo-athetotic hyperkinesis and epileptic fits, while after recovery from carbon-monoxide poisoning disorientation, confusion, and Parkinsonism may develop. While minor anoxic episodes during anaesthesia may not be so very uncommon, severe sequelae from them are fortunately rare; but the occasional post-anaesthetic case which lingers on in a vegetable existence is a tragic reminder of what can happen.

Carbon monoxide remains the commonest source of accidental poisoning, domestic or industrial. Its remarkable affinity for haemoglobin makes it dangerous even in circumstances where a person might reasonably feel safe—e.g., in a well, a garage, or, as happened in Cornwall last year, in the back of a moving car. The rapidity of its toxic effect will depend on its rate of production, the rate of air change in the atmosphere, and the amount of exercise performed by the person exposed. It is easy to see, therefore, that the circumstances in the well, with a petrol engine producing probably 6% of carbon monoxide in its exhaust gases, virtually no air change, and considerable exertion needed for climbing down and up 28 ft. (8.5 m.), would combine to produce the optimum conditions for rapid carbon-monoxide poisoning.

The layman often looks with scepticism on what may be described as the "scientific" defence or mitigation of a charge of fraud or "drunk in charge," while accepting without question the findings of a civil court or industrial inquiry. The legal findings in these two cases on the same day should underline the dangerous sequelae of cerebral anoxia from any cause.

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JURIES IN INJURY CASES

[FROM OUR LEGAL CORRESPONDENT]

In his presidential address to the Holdsworth Club of the Law Faculty of Birmingham University on March 14 Lord Justice Morris took as his theme the effect of the trend of public feeling on the administration of the law (*The Times*, March 15). In most cases, he said, damages for personal injuries are assessed by judges sitting alone without juries, but when a monetary payment had to be awarded as compensation for pain and suffering or for the loss of some of life's amenities the collective view of 12 citizens might be desirable. Even if only some such cases were tried with juries current public opinion as to the level of awards would be revealed.

When a Jury Sits

All indictable criminal offences must be tried by jury, and this has as a matter of history often revealed a divergence between the law and current public opinion. In the early nineteenth century, when hanging was still the penalty for stealing more than 40s., juries often refused to convict in the teeth of the evidence. In the late 1940s, when the minimum penalties for breaches of the Building Regulations were extremely severe, juries again often refused to convict even in cases where there was no real dispute that an offence had been committed.

In civil cases whether the trial is to be by jury or not is a matter of the discretion of the court. Either party can ask for a jury, and in some cases—for example, actions for libel—a jury if asked for will be ordered as of course. Before 1939 it was not rare to find juries trying personal injury cases, though it has never been as common in England as in the United States. During the war trial by jury was altogether suspended in civil cases, and afterwards except for actions for libel and breach of promise of marriage the jury has been very sparingly used.

While no doubt it would be helpful for Her Majesty's judges to get a cross-check on their awards of damages by an occasional jury's verdict, there are other sides to the picture. Jury service, though vital to the administration of criminal justice, can be very onerous for those who are called, even though jurors are now paid and can be compensated for loss and expense necessarily suffered or incurred for the purpose of enabling them to serve.

Damages

Moreover, far more actions for personal injuries are compromised than are ever fought out, with a consequent very great saving in legal costs and, since the introduction of Legal Aid, of public money. Such actions, broadly speaking, are only fought out when the plaintiff's advisers and the defendant's advisers differ too widely in their expectation of what the judge will award by way of damages. The assessment of the probable award is difficult enough when you have to consider not only the infinite variety of injuries but also the difference in what different individual judges are likely to award for identical injuries. If the tribunal for assessing the injury is a jury the task would be infinitely harder, if the experience of those who have to try to compromise libel actions by trying to decide what a jury is likely to award for injury to reputation is anything to go by.

Lord Justice Morris in discussing the problem stated that some people believed that judges sitting alone tended to make more generous awards than would be made by a jury. That is the converse of experience of the relative performance of juries in libel actions, and on appeals in personal injury actions judges' awards are sometimes found to be too low by the Court of Appeal as well as being sometimes found to be too high. While, as Lord Justice Morris said, "the courts must select those standards of behaviour by which right-thinking citizens would be content to be judged," the fact that there has been no demand from litigants or in Parliament for an increased use of the jury in personal injury actions surely indicates that right-thinking citizens are content to have the monetary compensation for their injuries, for which no money can in truth compensate them, assessed by the Queen's Bench judges. This is not to say that the public underrates the jury. There has been no widespread agitation to abolish trial by jury of indictable offences, and the jury is greatly valued by those charged with being drunk in charge of a motor-car.

Medical Notes in Parliament

INSANITY AND DIVORCE

The Divorce (Insanity and Desertion) Bill, a private member's measure sponsored in the House of Lords by Lord MESTON, was given a second reading there on May 20, after having passed the Commons. He explained that it did not create any new grounds nor extend any existing grounds for divorce. Its primary object was to give effect to recommendations of the Royal Commission on Marriage and Divorce by extending the types of treatment which enabled a husband or wife to obtain a divorce on the ground of the other's insanity, and by preventing the supervening insanity of a spouse from interrupting a period of desertion.

Certification Not to be Criterion

The Matrimonial Causes Act, in section 1(i)(d) provided that a husband or wife could obtain a decree of divorce on the ground that the other party was of incurably unsound mind and had been continuously under care and treatment for at least five years. A person was deemed to be under care and treatment only under four conditions, of which the principal feature was that all laid emphasis on the certification of the respondent. The Royal Commission pointed out that, while it was desirable to avoid certification so far as possible, this might result in considerable hardship for the patient's spouse. The patient might have spent some years in a mental hospital before certification; it might by that time be clear that his insanity was incurable; yet the spouse had to wait until the full five years' care and

treatment as a certified patient had elapsed before taking divorce proceedings. Relief would be completely denied when the patient, though incurably insane, continued to keep his voluntary status, because the need for certification never arose. The Royal Commission therefore thought that treatment as a voluntary patient should be recognized as care and treatment whether under the Mental Treatment Acts or in an institution outside those Acts. In other words, certification was no longer to be the criterion. Accordingly, Clause I(1)(a) of the Bill provided that care and treatment in any hospital or other institution should be deemed care and treatment for the purpose of divorce proceedings on the ground of insanity. This provision alluded only to treatment for mental illness, and covered treatment only in hospitals and institutions recognized by public authorities; it did not cover treatment as a single patient in charge of a doctor, matron, or other person.

Comparable treatment in a hospital or institution in any other country was covered in subsection (b); and clause I(2) provided that a certificate by the appropriate Service authority should be conclusive evidence in the case of persons serving in the Forces.

Insanity Not to Interrupt Desertion

Clause 2 dealt with a different matter. A petition for divorce (or judicial separation) could be based on desertion without cause for a period of three years. The fact that a spouse had been certified as insane subsequent to the initial act of desertion had raised a doubt whether he had been capable of a continuing intention to desert. The clause, following a recommendation of the Royal Commission, provided that desertion should be deemed not to have been interrupted by the insanity of the deserting spouse if it appeared to the court that desertion would probably have continued if he had not become insane.

Lord MERRIMAN, President of the Probate, Divorce and Admiralty Division, commended the Bill as recognizing the modern opinion that certification, so far from being the first, should be the last resort in mental illness. Lord MORTON OF HENRYTON, who was chairman of the Royal Commission, recalled that one witness had pressed on them the words of the marriage service—"In sickness and in health, as long as you both shall live"—and pointed out that the person of unsound mind had committed no matrimonial offence and could not help it. The Commission could not agree with the views of the witness. They thought this ground for divorce should be retained, with the two essential safeguards of evidence of incurably unsound mind and a period of five years' continuous treatment. Lord DENNING would have liked to see the Bill go further and provide that insanity should not be a defence to cruelty any more than it was to desertion.

Lord CHESHAM, Lord-in-Waiting, expressed the Government's view that the Bill made some timely and useful reforms. It was clearly desirable to take into account the new outlook on mental illness and the efforts now made to encourage a mentally ill person to become a voluntary patient.

PURCHASE TAX ON DRUGS AND MEDICINES

During the debates on the committee stage of the Finance Bill, Mr. G. NABARRO (Kidderminster, Con.) endeavoured on May 20 to secure, by an amendment to the First Schedule, a reduction from 30% to 15% on "drugs and medicines, manufactured or prepared, except toilet preparations" (Group 33).

Household Remedies

He said that only a small part of the drugs and medicines which carried tax fell within the ambit of "drugs and medicines." The wholesale value was about £37m., and the amount of tax raised was about £11m., of which about £1,500,000 was in respect of proprietary drugs and medicines prescribed within the Health Service that found its way back to the Treasury. The Conservative Party had from the outset been opposed to the tax on drugs and medicines. Many of those which attracted tax were generally known as household remedies; they were proprietary brands, readily available, and were found in nearly every household medicine chest. They were, he claimed, essential commodities, and might reasonably be compared with foodstuffs. To tax them was to place a direct tax on the promotion of good health or the avoidance of illness. The position had been made complicated by the fact that a large number of proprietary drugs and medicines were exempt. Dispensing packs were specifically exempted, but the same products in a smaller or different size for sale to the public separately attracted the tax. The time had come to consider abolishing—or at least going half-way this year, as the amendment proposed—a tax which was inimical to the public. If everyone who suffered a cut or burn or a minor ailment resorted at once to the Health Service, doctors' surgeries would be cluttered up. Self-medication in minor ailments was something that every M.P. ought to support.

Dr. BARNET STROSS (Stoke-on-Trent, Central, Lab.) thought there were some things that merited taxation. He mentioned as examples phenobarbitone, petroleum jelly, and aspirin, all of which could be prescribed and were not taxed, and all of which could be obtained under another name at much greater cost, and said he would find it difficult to deny the Treasury the right to say that these more costly varieties should be taxed. But it was easy to find gross anomalies. It was absurd that because a ring was put round the corrosive material that softened a corn the pad or plaster should become chargeable. Even the mustard leaf on a bandage became chargeable, though ordinary forms of bandage and lint were not. He hoped the Treasury would try to remove some of the obvious anomalies; but if the Government were to seek to remit taxation on proprietary goods advertised to the public at large there would be a majority of the House against them.

Principle of Exemptions

Mr. J. E. S. SIMON, Financial Secretary to the Treasury, opposing the amendment, said it would mean a loss in revenue of £5,500,000. If the aim was to approach something like a uniform tax on a wide range of goods, they should consider carefully before starting to erode the width of the base of purchase tax—which was what the amendment would do. The tax combined the need to reconcile the two principles—first, to raise revenue; and, secondly, to ensure that there was no deprivation of proper medication. The way that was done was through exemptions. In Group 33(b) exemption was given to official drugs and medicines—preparations composed of items that appeared in standard publications, of which the *British Pharmacopoeia* was the principal one, if sold in a non-proprietary and unbranded form. The same group exempted official preparations in a branded or proprietary get-up when sold in special packs for dispensing purposes only. In Group 33(c) was a long list of essential drugs or medicines, whether or not marketed in a proprietary form. This list was kept up to date by constant advice from the Ministry of Health experts. Anyone who needed it got his medicine and drugs tax-free, yet there was a large residual expenditure on drugs and medicines of a kind that were properly subject to taxation and produced a large revenue that could not be forgone.

The amendment was rejected, after the Opposition had refused Mr. Nabarro leave to withdraw it, by 233 votes to nil.

ANSWERS TO QUESTIONS

Law on Suicide

Mr. KENNETH ROBINSON (St. Pancras, North, Lab.) asked the Home Secretary on May 22 what further consideration he had given to the legal aspect of suicide and attempted suicide; and if he was aware that the law of England and

Wales stood almost alone in regarding such acts as criminal. Mr. R. A. BUTLER replied that he was pursuing his study of this problem, which had practical aspects of no less importance than its legal aspects. He was not yet ready to reach a conclusion upon it.

Mr. ROBINSON pointed out that a joint committee of the B.M.A. and the Magistrates' Association set up to examine this subject had reported in favour of a change in the law in the direction he was suggesting, and that this report was unanimously accepted by the council of the Magistrates' Association. In view of this weighty opinion, he asked, would the Home Secretary make an early decision? Mr. BUTLER said he knew of the report, and he was also aware of various other considerations. This was a very difficult subject, but he would consider what Mr. Robinson had said.

Mr. GORDON WALKER (Smethwick, Lab.) invited the Home Secretary to agree that there were no real religious grounds for the law, and that it was due to a judicial decision about a hundred years ago. Was there not a great deal to be said for bringing English law into line with that of other countries? Mr. BUTLER said he had studied the position in other countries, and also the statistics of convictions. In 1956 proceedings were brought in 613 cases out of 5,000 or more, and over 90% of these resulted in probation and very few in sentences of imprisonment. In a minority of cases, without the power they had now, they might not be able to achieve the desired results. So, on the facts, it was a difficult question to decide.

Mr. ROBINSON suggested that other provisions in the law in regard to breach of the peace and mental health were sufficient to deal with the cases the Home Secretary had in mind. Mr. BUTLER replied that the Government's approach to mental health "is at present actual." It was against that background that he was examining it.

Wolfenden Report

Mr. D. DONNELLY (Pembroke, Lab.) asked the Home Secretary if he could make a statement on the Government's policy towards the Wolfenden Report on Homosexuality and Prostitution. Mr. BUTLER stated that many representations had been made since the report was published. Some of them were in support of the committee's recommendations, but others were strongly critical. This applied both to the main recommendations on homosexual offences and to those on prostitution. It was clear that the committee's recommendations had stirred public opinion widely and deeply, and he would not propose to decide on a future course of action until that opinion had had the fullest opportunity of expressing itself.

Mr. DONNELLY urged that the House had a certain responsibility to discuss these topics; and asked whether, if the motion which Mr. Montgomery Hyde had proposed on this subject for June 13 was not reached, it would be possible to provide time before the summer recess to test the opinion of the House. Mr. BUTLER said he had always taken the view that before coming to a final decision on every aspect of the report it would be helpful to have a debate; in fact, it was important that it should be so. He could not say what fortune the motion on June 13 [a private members'day] would have. In any case, he would always be ready to take part in any discussion if an opportunity could be offered.

Mr. GORDON WALKER pressed the point that the Government should find time for a debate. This was a matter of public policy, but the Government had first responsibility. He agreed that the House should not rush into a decision, but public opinion would be guided and crystallized to some extent by what was said there. Mr. BUTLER said that so far he had not had an opportunity to find an occasion in Government time, and he had not yet heard from the Opposition that they would do this in the time available to them. But as there was no controversy so far as discussion was concerned they could all see what opportunity might be found.

Welsh Teaching Hospital

Mr. H. R. GOWER (Barry, Con.) asked the Minister of Health on May 19 when he hoped to be able to authorize the commencement of the Welsh Teaching Hospital. Mr. R. THOMPSON, the Parliamentary Secretary, replied that the Minister was not in a position at present to make a statement. The date of commencement of building must depend on the completion of detailed architectural plans, which would take some two to three years yet, and on the availability of finance then.

Paralytic Poliomyelitis

Mr. S. VIANT (Willesden, West, Lab.) asked the Minister of Health what was the attack rate of paralytic poliomyelitis per 100,000 of the population aged over 20 years; and what was the death rate of paralytic poliomyelitis in that age group. Mr. D. WALKER-SMITH informed him on May 20 that separate figures related to age 20 were not available. For ages 15 and over the attack rate in England and Wales in 1957 was 3.1 per 100,000, and for ages 25 and over 2.7 per 100,000; death rates were 0.3 in each case.

Mr. VIANT also asked how many children per 100,000 of the population under 15 years of age contracted paralytic poliomyelitis in each of the years 1950 to 1957, and was given the following figures: 39.4, 10.1, 18.7, 19.3, 9.4, 25.0, 11.1, and 20.3 respectively.

Pay of Hospital Medical Staff

Lord DOUGLAS OF BARLOCH asked the Government in the House of Lords on May 20 what was the present scale of remuneration of registrars, senior registrars, junior hospital medical officers, senior hospital medical officers, and consultants (full-time) employed in the National Hospital Service, and what were the corresponding figures recommended by the Spens Committee increased proportionately to the cost of living.

Lord STRATHCLYDE, Minister of State, Scottish Office, replied that the scales were respectively £935 to £1,061; £1,210 to £1,540; £852 to £1,182; £1,653 to £2,126; and £2,205 to £3,255. Consultants could also receive distinction awards varying from £500 to £2,500. It would be impracticable to give proportional increases in relation to the cost of living because no official cost-of-living index appropriate to persons in those salary groups was available. In any case the Spens Committee considered that regard should be had not only to changes in the value of money but to the increases in income since 1939 in both the medical and other professions. The general question of the remuneration of doctors in the National Health Service was under consideration by the Royal Commission.

MEDICAL ACT AMENDMENT SOUGHT

Mr. J. B. HYND (Sheffield, Attercliffe, Lab.) has given notice of his intention to seek leave on June 10 to introduce the Medical Act, 1956 (Amendment) Bill, to amend the provisions of Part II of the 1956 Act relating to the experience required for full registration and to applications for provisional registration, and of the First Schedule to the Act relating to fees, expenses, and allowances.

Universities and Colleges

UNIVERSITY OF CAMBRIDGE

In Congregation on March 22 the following degrees were conferred:

M.CHIR.—T. W. Rowntree, E. J. C. Wynne.
M.B., B.CHIR.—D. E. Side.
M.B.—*(By proxy)* R. C. Dobbie.

UNIVERSITY OF GLASGOW

On April 26 the degree of M.D. was conferred on:

B. Camber, Ella I. McNaught, *W. McNaught, *A. J. O'Hea, *A. A. Robin.

*With commendation.

UNIVERSITY OF LONDON

On March 26 the Senate awarded the degree of M.D. to H. B. Hewitt and the degree of M.S. to A. J. Davies.

UNIVERSITY OF LEEDS

O. P. Edmonds was approved at the March examination for the degree of M.D.

UNIVERSITY OF SHEFFIELD

Dr. J. E. M. Whitehead has resigned his appointment as honorary Lecturer in Bacteriology.

ROYAL COLLEGE OF PHYSICIANS OF LONDON

At a quarterly comitia of the College held on April 24, with the President, Professor Robert Platt, in the chair, the following representatives were appointed: Dr. W. S. C. Copeman on the committee of management of the Chelsea Physic Garden; Dr. N. G. Harris on the council of the National Association for Mental Health for 1958; and Dr. J. Forest Smith and Dr. E. F. Scowen on the council of the Imperial Cancer Research Fund until April, 1961.

Licences to practise were conferred upon the following 145 candidates who have passed the final examination in medicine, surgery, and midwifery of the Conjoint Board, and who have complied with the by-laws of the College:

T. R. Abbott, H. B. Bailey, R. Barker, J. D. Barrett, J. M. Beeley, J. T. Bench, C. Berry, N. D'E. G. Best, B. Bhattacharya, Margaret A. Birchall, J. M. Black, Sarah M. E. Blatch, Natalie Bogdan, Mary-Ann M. Bolt, M. C. Bott, Patricia M. Bradford, R. W. Bramwell, J. F. Branton, J. Brice-Smith, T. R. Bull, Shirley F. C. Burrell, Christine M. Butler, A. J. G. Campbell, P. A. Carter, R. Chapple, S. E. Cheah, J. H. Chilman, Daphne C. K. Clarke, Marion Coates, R. D. Cohen, D. M. A. Cowie, Sheila M. Crawshaw, R. H. I. Crockatt, Patricia E. Crome, P. G. Darby, A. H. Davies, Ann V. Daws, D. D. Devine, E. F. Doleman, H. S. Donnelly, E. E. Douck, Jean G. Doughty, D. C. Dukes, J. G. Edwards, L. A. Emanuel, E. R. Emmanuel, G. Evans, Patricia Farren, F. J. Fawcett, A. V. Fox, Ruth Frank, I. Freedman, P. M. Fullman, R. Gaertner, J. R. Geddes, D. W. R. George, G. R. Gerson, D. H. Gill, J. E. Godrich, M. J. Goggin, B. Goodhead, Dorothy R. Gordon, A. J. Gregory, Janet M. Guenault, K. C. Hammond, J. T. Harries, J. S. G. Hayes, G. D. Hayter, Elizabeth M. Hedges, Gillian C. Henly, J. R. Heron, A. B. Hewitt, Nitza F. Hill, L. J. Hipkin, M. Hopwood, Judith Hornung, G. R. Horton, Margaret E. Hughes, D. J. Hunt, G. B. Hunt, D. A. Hutchinson, Sheila M. V. Jeffery, R. D. T. Jenkin, G. I. John, G. W. Jones, J. F. Kane, W. E. Kearns, Delia M. Kenyon, J. O. Kilby, K. G. Korsah, O. Kusi-Mensah, Hilary R. G. Lennox, A. J. Lupin, D. R. McCoy, A. Magrath, R. T. F. Maguire, G. M. Makhlouf, J. Martin, D. R. Matthes, June Mills, A. B. Morphy, Evelyn J. Moss, Frances A. Musson, C. R. Neequaye, D. Negus, A. D. Noble, C. F. W. Palmer, A. J. Pechal, N. Peters, Elizabeth J. Porter, A. Powell, P. R. Preston, J. D. Price, B. J. Prout, D. J. Puddifant, C. D. P. Rhodes, Margaret Richardson, H. P. Rikard-Bell, C. J. Roberts, E. J. R. Rossiter, Naomi J. Sase, M. D. Sidell, J. B. Sorapure, B. R. Sparke, C. G. Stephenson, Pamela M. Stracey, R. C. Swan, M. H. Sykes, M. A. E. Symonds, D. J. E. Taylor, B. M. Thomas, J. Ll. E. W. Thomas, Winifred Tooby, J. C. Uzoma, C. W. Venables, M. T. Ward, Judith C. R. Wardle, Dorothy West, A. J. Whitley, Barbara J. Willmer, D. N. Wood, W. D. R. Writer, J. D. Wyatt, S. Y. Yip, D. A. Young.

The following diplomas were conferred, jointly with the Royal College of Surgeons of England:

DIPLOMA IN CHILD HEALTH.—G. P. Anthony, C. P. Anyon, Mary C. Armstrong, Saraswati Arora, K. Arunlakshana, C. S. Ayoub, P. A. Barker, N. Beenstock, Edith Bergel, Marjorie L. Bowen, K. D. Boyd, Marjory H. Boyle, Margaret E. Broughton, Alison G. H. Brown, T. F. Bushby, Josephine H. Calder, Enid G. Carson, H. J. W. Cleeve, I. Crawford, Martha E. N. Davies, H. Davis, W. S. de Silva, Patricia A. Dinkel, Patricia J. Dockery, Sheila M. Foster, Lise L. Fowle, Gillian M. Gandy, M. B. Gee, S. S. Ghatak, D. C. Gill, Catherine E. Hall, S. M. Haneef, B. R. Hardwick-Smith, Audrey M. Hillary, B. Ibrahim, C. Ioannou, M. L. M. Izzadeen, R. B. Jahina, C. R. Jayachandra, Emily M. Kerr, Hilda Koilpillai, Kathleen M. Laing, Kathleen M. Lamont, Alice Latham, H. A. McClelland, Kathleen L. MacGregor, Irene E. McLaren, Dorothy Mainwaring, J. R. MacG. Millar, J. N. S. Mitchell, Wendy L. Mitchener, Y. P. Narula, E. I. F. Nashawati, P. O. Nicholas, N. J. O'Doherty, M. J. Page, Dolly I. Pakshong, K. Paramathypathy, F. B. W. Parker, M. D. Parker, M. W. Partington, Veronica Pearson, J. D. W. Peck, Valerie J. Perkins, T. G. J. Phillips, Philine T. Pieris, Mavis M. Polkinghorne, Srijayadevi Ponnudurai, Dorothy H. E. Ramsay, S. K. Ray, Pamela A. M. Rendell, Raine E. I. Roberts, Jill P. Rosser, S. K. Roy, Sophie Sash, Promod C. Sharma, M. Shavitsky, W. H. Shaw, P. F. Sheppard, M. H. Lees, S. L. Shrikhande, J. A. B. Spalding, J. N. Standring, H. Stark, Averil M. Stedeford, R. McK. Sutherland, K. H. Tan, Frances C. Thomson, Elizabeth M. Tilsen, M. W. Tisdall, Anne E. Treharne, Y. K. Tseung, Pia M. Unger, S. K. Vohra, Barbara Ward, Jean M. Watkins, M. A. Wenig, Catherine M. White, R. G. M. Whittaker, R. M. Whittington, A. Wijenaike, F. Wilson, Maidie E. Wilson, S. E. A. Wyner, Pamela M. Zinkin.

DIPLOMA IN OPHTHALMOLOGY.—A. P. Barclay, B. J. Bowden, B. D. Coote, C. C. Ewing, T. P. Griffith, W. M. Higginbottom, Elizabeth D. Jamie, R. V. Kotnis, C. G. McEwen, I. A. Mackie, N. E. L. Margetson, I. A. Mir, G. A. I. Namsoo, Margaret C. W. Neilson, J. B. Parton, Than Pe, C. O. Quarcoopome, Dev Raj, T. V. Ranganathan, A. P. Sah, L. F. Shanahan, Froma Somerville, P. Taylor, D. O. Tonkin, Ursula Walters.

Diplomas in Laryngology and Otology, in Physical Medicine, and in Tropical Medicine and Hygiene were granted, jointly with the Royal College of Surgeons of England, to the successful candidates whose names are printed below in the report of the meeting of the Royal College of Surgeons of England held on April 17.

ROYAL COLLEGE OF SURGEONS OF ENGLAND

At a meeting of the Council of the College held on April 17, with Sir James Paterson Ross in the chair, Mr. P. C. Williams and Dr. F. C. Chesterman were appointed Imperial Cancer Research Fund Lecturers for 1958.

Diplomas of Fellowship were granted to P. M. Marnie (Sydney) and M. F. Sturridge (Angmering-on-Sea).

The following diplomas were granted, jointly with the Royal College of Physicians of London:

DIPLOMA IN LARYNGOLOGY AND OTOLOGY.—A. D. Soysa.

DIPLOMA IN PHYSICAL MEDICINE.—A. M. Bain, J. D. K. Palmer.

DIPLOMA IN TROPICAL MEDICINE AND HYGIENE.—A. J. Berman, T. K. Bose, J. K. Chakravarti, D. D. E. W. de Alwis, U. Fornari, M. C. Gupta, M. Haque, H. T. Heah, M. D. Heyman, F. N. C. Ho, M. H. Husaini, R. T. Jensen, P. V. Krishnamurti, L. Langlo, G. R. L. Lyons, W. R. McKibben, P. D. Marsden, R. J. Onyango, E. S. Pillay, Nargis N. J. Rana, B. N. Roy, L. Saint-Arnaud, M. Y. Siddiqui, J. P. Soonawalla, S. Thanikasalam, M. McC. Wilson, C. M. Wylie.

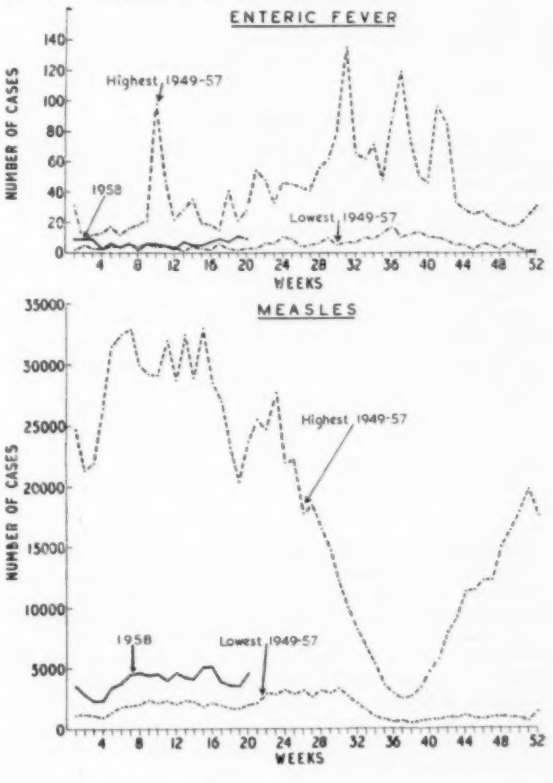
ROYAL COLLEGE OF PHYSICIANS OF IRELAND

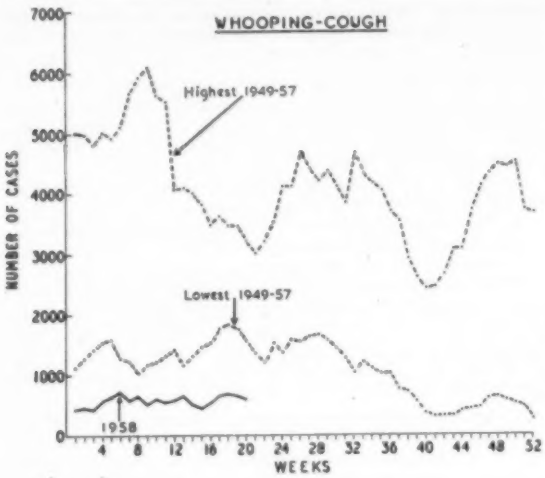
At a meeting of the College held on March 28 the President, Dr. F. J. O'Donnell, admitted the following candidates to the Licence in Medicine and Midwifery: J. G. Bailie, Efiong Ekpo, J. R. McClean, Frances M. U. Power, S. A. Ramjanally, R. F. Rampersad, J. S. Rautenbach, and Ewa Wohnout.

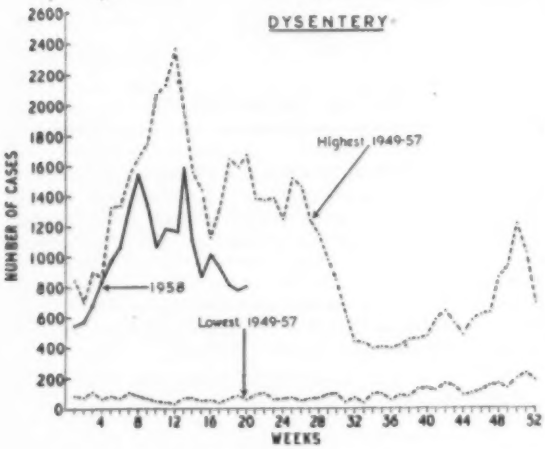
Vital Statistics

Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1949–57 are shown thus ------, the figures for 1958 thus ———. Except for the curves showing notifications in 1958, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.







Week Ending May 17

The chief feature of the returns in England and Wales during the week ending May 17 was a rise of 987 in measles, from 3,572 to 4,559; other rises in incidence were 43 for scarlet fever, from 706 to 749, 38 for food-poisoning, from 159 to 197, and 32 for dysentery, from 771 to 803, while the largest falls were 61 for acute pneumonia, from 304 to 243, and 47 for whooping-cough, from 652 to 605.

The largest rises in the notifications of measles were 153 in Lincolnshire, from 120 to 273 (South Kesteven R.D. 54, West Kesteven R.D. 60), 106 in Westmorland, from 8 to 114 (South Westmorland R.D. 106), 92 in Norfolk, from 74 to 166 (Norwich C.B. 110), 87 in London, from 349 to 436 (Islington 164, St. Pancras 57). Small fluctuations were reported in the local returns of scarlet fever and whooping-cough. Only 1 case of diphtheria was notified compared with 4 in the preceding week.

The notifications of acute poliomyelitis numbered 16, and these were 1 fewer for paralytic and 3 fewer for non-paralytic cases than in the preceding week. The largest returns were 3 cases each in Middlesex and in Surrey.

No notable variations were reported in the various outbreaks of dysentery. The largest centres of infection during the week were Lancashire 188 (Liverpool C.B. 42, Manchester C.B. 32, Oldham C.B. 40), Yorkshire West Riding 174 (Sheffield C.B. 41, Barnsley C.B. 23, Leeds C.B. 16, Wakefield C.B. 12), London 67 (Southwark 13, Wandsworth 12), Cheshire 51 (Northwich R.D. 19, Birkenhead C.B. 13), Staffordshire 42 (Cannock U.D. 26), Durham 31 (South Shields C.B. 12), Warwickshire 24 (Birmingham C.B. 20), and Surrey 20 (Godstone R.D. 10).

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending May 10 (No. 19) and corresponding week 1957.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1958					1957				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria ..	4	0	2	0	2	3	0	3	0	
Dysentery ..	771	74	193	7	2	669	31	237	17	
Encephalitis, acute	6	1		0		5	1		0	
Enteric fever:										
Typhoid ..	4	0	1	0		1	0	1	0	
Paratyphoid ..	7	1	2(B)	0	3(B)	1	0	1	0	
Food-poisoning ..	159	32	15	3		150	15	20	1	
Infective enteritis or diarrhoea under 2 years				11	25				20	11
Measles *	3,572	349	170	50	3	18,265	1169	231	251	278
Meningococcal infection	16	3	6	1	1	23	1	14	0	
Ophthalmia neonatorum	23	2	4	0		39	1	6	0	
Pneumonia † ..	304	34	181	23	2	392	26	145	11	13
Poliomyelitis, acute:										
Paralytic ..	13	2	2	2	7	39	5	3	1	2
Non-paralytic ..	7	1				30	2			
Puerperal fever § ..	220	29	9	1		207	38	6	1	
Scarlet fever ..	706	53	71	28	12	497	41	67	30	16
Tuberculosis:										
Respiratory ..	565	57	89	21		647	77	417	15	
Non-respiratory	67	5	23	2		99	7	12	2	
Whooping-cough ..	652	21	61	7	22	2,362	88	299	9	42

DEATHS	1958					1957				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria ..	0	0	0	0	0	No comparable figures available.	0	0	0	0
Dysentery ..	1	0		0			0		0	
Encephalitis, acute		0			0		0			0
Enteric fever ..	0	0	0	0			0	0	0	
Infective enteritis or diarrhoea under 2 years	5	0	0	0	1		0	1	0	0
Influenza	19	1	0	0	0		0	0	0	1
Measles		0	0	0	0		1	0	0	0
Meningococcal infection		1	0				0	0		
Pneumonia ..	434	30	25	10	9		28	19	9	10
Poliomyelitis, acute	1	0		0	0		0			0
Scarlet fever ..		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory ..	82	3	5	2	2		2	12	1	6
Non-respiratory		1	1	0	1		3	0	0	1
Whooping-cough ..	0	0	0	0	0		0	1	0	0
Deaths 0–1 year ..	306	26	43	3	16		30	29	10	14
Deaths (excluding stillbirths) ..	9,005	723	545	90	147		663	605	107	187
LIVE BIRTHS ..	14,792	1227	1132	243	365		1265	1036	244	427
STILLBIRTHS ..	288	12	23				31	36		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

Bristol University.—Professor C. BRUCE PERRY, the professor of medicine at Bristol, has been appointed Pro-Vice-Chancellor of the University for three years from August 1. Dr. J. Boss has been appointed to a lectureship in physiology, and Mr. K. D. J. VOWLES to one in surgery.

Royal Society of Health.—Lord COHEN OF BIRKENHEAD has been elected president of the Royal Society of Health in succession to the late Lord PERCY OF NEWCASTLE. Lord Cohen is the first medical man to hold this office. Speaking of the diverse elements of the medical profession, Lord Cohen said at the Society's annual luncheon last week: "Many organizations have developed which represent the interests of special groups. Whatever administrative convenience these provide—and we must all concede they are good—there is yet the important function of integrating all disciplines which have a contribution to make to the health of the nation. It is here that the Royal Society of Health plays a unique role."

Order of St. John of Jerusalem.—Among those invested as Knights of the Order of the Hospital of St. John of Jerusalem on May 20 by the Grand Prior of the Order, the DUKE OF GLOUCESTER, at St. James's Palace, were Sir ARTHUR PORRITT, Surgeon Vice-Admiral Sir ALEXANDER INGLEBY MACKENZIE, Dr. C. S. C. PRANCE, Colonel C. H. S. REDMOND, Dr. W. RITCHIE RUSSELL, Dr. J. T. WHITLEY, and Dr. R. V. S. COOPER.

Gairdner Foundation.—The Gairdner Charitable Foundation, of Ontario, announces two types of international award. The first, the Foundation's "award of merit," is a four-yearly prize of $25,000 for the person or group of persons who in the Foundation's view have made the most outstanding contribution in the field of arthritic, rheumatic, or cardiovascular disease. The second type of award consists of prizes of $5,000 for up to five persons a year for their outstanding achievements in the same field. The first awards will be made this year. Further details may be obtained from the general secretary, Gairdner Charitable Foundation, 320, Bay Street, Toronto.

Beit Memorial Fellowships.—The Trustees of the Beit memorial fellowships for medical research in their report for 1957–8 announce that Professor G. F. MARRIAN, F.R.S., has been elected a member of the advisory board in place of Dr. C. H. ANDREWES, F.R.S., who retires after 14 years. The following elections to junior fellowships (£900 a year) were made: Dr. PHOEBE M. COTES, at University College Hospital Medical School, London; Dr. J. G. NICHOLLS, at the department of physiology, University College, London; Dr. G. M. A. GRAY, at the Lister Institute of Preventive Medicine, London; Mr. J. B. GURDON, at the department of zoology and comparative anatomy, Oxford University; Dr. MARGARETHE M. A. HOLZBAUER, at the department of pharmacology, Edinburgh University; and Dr. F. H. TAYLOR, at the department of chemistry, Imperial College, London.

London University.—Dr. E. C. WARNER, physician to Charing Cross Hospital, has been elected to the Senate. At the Foundation Day ceremony on November 21, Sir ARCHIBALD GRAY is to receive the honorary degree of Doctor of Laws, and Sir ALEXANDER TODD, F.R.S., the honorary degree of Doctor of Science.

Sheffield University.—Dr. P. F. HARRIS and Dr. M. TAYLOR have been appointed lecturers in anatomy. Miss E. L. JERVIS has been appointed a lecturer in physiology. Dr. MARGARET M. PLATTS and Dr. D. HOBSON have been appointed part-time honorary lecturers in medicine and bacteriology respectively, and Dr. J. P. P. BRADSHAW and Dr. W. L. TONGE have been appointed part-time clinical teachers in neurology and psychiatry respectively.

Margaret de Sousa Deiro Fund.—By a recent Order of the Charity Commissioners the scope of this Fund, which was originally confined to assisting indigent gentlewomen with early pulmonary tuberculosis, has been widened, so that surplus funds may now be used for the care, rehabilitation, and aftercare of indigent women who have, or have had, any kind of chest disease. The fund may make grants to cover the cost of treatment, when this cannot be carried out in suitable conditions under the N.H.S., and towards convalescent holidays. Details may be obtained from the Fund's Office, 1, New Court, Carey Street, Lincoln's Inn, London, W.C.2.

Polar Medals.—Medical members of the Commonwealth Trans-Antarctic Expedition who received polar medals from the QUEEN this month were Dr. G. W. MARSH (clasp to his medal), Dr. R. GOLDSMITH, and Dr. A. F. ROGERS.

B.M.A. Glasgow Office.—The new address of the B.M.A. Glasgow Regional Office is 9, Lynedoch Crescent, Glasgow, C.3 (Telephone: Douglas 1862/3/4).

Chief Nursing Officer.—Miss K. A. RAVEN has been appointed Chief Nursing Officer at the Ministry of Health and will succeed Dame ELIZABETH COCKAYNE on July 1. Miss Raven was formerly assistant matron at St. Bartholomew's Hospital, London, and matron of Leeds General Infirmary. Since October she has been Deputy Chief Nursing Officer at the Ministry.

Society of Physicians in Wales.—The annual meeting was held at the Hotel Portmeirion, Merionethshire, on May 9 and 10.

Civil Consultant to R.A.F.—Professor J. B. KINMONTH, director of the surgical unit at St. Thomas's Hospital, has been appointed honorary civil consultant in peripheral vascular surgery to the Royal Air Force.

Sir Kenneth Cowan, Chief Medical Officer, Department of Health for Scotland, is leading the U.K. delegation to the eleventh World Health Assembly. The Assembly is being held at Minneapolis from May 25 to June 14.

Dr. Macdonald Critchley.—On the occasion of the recent inauguration of the new building of the Medical Society of the University of Aix-Marseille, the honorary degree of Docteur en Médecine was accorded to Dr. MACDONALD CRITCHLEY.

Professor W. T. J. Morgan, F.R.S., deputy director of the Lister Institute, has been appointed a member of the Minister of Supply's advisory council on scientific research and technical development.

Dr. G. H. Wright, lecturer in anatomy at Cambridge, has been elected into an official fellowship at Clare.

Professor F. J. Fenner, who has been professor of microbiology at the Australian National University, Canberra, since 1949, was recently elected a Fellow of the Royal Society. In the last few years his studies have been mainly on the tubercle bacillus and vaccination against the disease, and on the epidemiology of myxomatosis in wild rabbits.

Professor E. G. L. Bywaters, professor of rheumatology at the Postgraduate Medical School of London, is going to Yugoslavia to lecture on the prevention of rheumatism. He will be away from about June 3 to 24.

COMING EVENTS

Dental and Medical Society for the Study of Hypnosis.—Inaugural meeting of the Midlands Branch, June 1, at the Birmingham Medical Institute. Also week-end course in hypnotherapy, June 21–22, at the Queen Elizabeth Hospital, Edgbaston. Details from Mr. S. N. TINKLER, 151, Lichfield Street, Walsall, Staffs.

Leeds Medical Exhibition.—June 2–6, at the Town Hall, Leeds. Open Monday 2.30 p.m.–7 p.m., Wednesday 11.30 a.m.–7.30 p.m., Tuesday, Thursday, and Friday 11.30 a.m.–6.30 p.m. Professor S. J. HARTFALL will open the exhibition at 2.45 p.m. on June 2.

Radio.—"The Mind and the Skin," B.B.C. Home Service, June 4 at 9.15 p.m.

Comité de la Neutralité de la Médecine en Temps de Guerre.—International congress in Paris, June 5–7. Details from the committee, 37, Rue de Bellechasse, Paris, 7.

St. Helen's Cake Fair.—The fifth Cake Fair will be held on June 6 in the forecourt of St. Helen's Church, London, E.C.3. The proceeds will be divided between the Imperial Cancer Research Fund and the Church Restoration Fund.

Ernestine Henry Lecture.—Dr. J. N. MORRIS will lecture at the Royal College of Physicians on June 10 at 5 p.m. His subject will be "Coronary Heart Disease and Occupation."

British Society for Immunology.—Meeting at the National Institute for Medical Research, June 13 and 14. The meeting will include a symposium on "Gammaglobulin and Antibodies." Details from Dr. R. G. WHITE, The London Hospital, London, E.1.

Faculty of Anaesthetists.—Scientific meeting at the Royal College of Surgeons on June 14 (starting at 10 a.m.) on "Shock and Allied Phenomena."

Fédération des Sociétés de Gynécologie et d'Obstétrique de la Langue Française.—18th congress, in Paris, June 15–17. Details from Dr. ROBEY, 3, Avenue St. Honoré d'Eylau, Paris, 16.

Course in Endocrinology.—June 16–21, at the Hôpital Laennec, Paris. Details from Dr. ALBEAUX-FERNET, Hôpital Laennec, 42, Rue de Sèvres, Paris, 7.

Friends of Vellore.—Mr. PAUL BRAND, F.R.C.S., will lecture on "Reconstructive Surgery in Leprosy" at 5.15 p.m. on June 18 at the Royal Society of Medicine.

Postgraduate Dinner.—Annual dinner and dance of the Postgraduate Medical School and Hammersmith Hospital Association, July 4, at Park Lane Hotel, 7.45 p.m. Details and tickets from Dr. D. ABELSON, Department of Medicine, Postgraduate Medical School of London, Ducane Road, London, W.12.

NEW ISSUES

SPECIALIST JOURNALS AND ABSTRACTS

The journals listed below are obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1.

Journal of Clinical Pathology.—Issued six times a year (£4 4s. annually). The new issue (Vol. 11, No. 3) includes:

THE NATURE, DETERMINATION, AND CLINICAL IMPORTANCE OF BLOOD IODINE: A REVIEW. J. D. Acland.
THE DEMONSTRATION OF INTRAVASCULAR HAEMOLYSIS BY MEANS OF SERUM PAPER ELECTROPHORESIS AND A MODIFICATION OF SCHUMM'S REACTION. F. C. Neale, G. M. Aber, and B. E. Northam.
THE VALUE OF LABORATORY TESTS IN HYPOTHERMIA. Peter I. Reed and Ketty E. Gavrilescu.
THE ROUTINE ASSAY OF B_{12} IN SERUM. A. I. Tiffin and G. M. Williamson.
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GIANT CELL GRANULOMATA IN REGIONAL LYMPH NODES OF CARCINOMA. G. A. Gresham and A. G. Ackerley.
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SOME OBSERVATIONS ON THE COAGULATION DEFECT IN VITAMIN K DEFICIENCY. A. S. Douglas.
THE ABSENCE OF ABNORMAL HAEMOGLOBINS IN 500 OUT-PATIENTS IN BRITAIN. J. Q. Matthias.
FATAL LISTERIA MONOCYTOGENES MENINGITIS IN A CHILD AGED 3 MONTHS. G. C. Turner, I. M. P. Dawson, and Elizabeth Pryce-Jones.
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SOCIETIES AND LECTURES

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Monday, June 2

●INSTITUTE OF OBSTETRICS AND GYNAECOLOGY.—At Chelsea Hospital for Women, 4.30 p.m., Mr. F. Denny: Post-operative Complications in Gynaecological Practice.
MARLBOROUGH DAY HOSPITAL.—8.15 p.m., Miss Olive Cram: On the History, Organization, and Function of the Child Care Committees.

Tuesday, June 3

HEATHERWOOD ORTHOPAEDIC HOSPITAL.—8.30 p.m., Dr. H. M. Sinclair: Osteoporosis.
INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. R. H. Meara: Bullous Eruptions.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Dr. Howard Burchell: Uncommon Heart Diseases.

Wednesday, June 4

INSTITUTE OF CARDIOLOGY.—At Barnes Hall, Royal Society of Medicine, 5 p.m., St. Cyres Lecture by Dr. Howard Burchell (U.S.A.): Studies of Pulmonary Hypertension in Congenital Heart Disease.
INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. H. Haber: Histopathology of Vesicular and Bullous Eruptions.
INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. P. J. Lawther: Air Pollution and Disease.
LONDON UNIVERSITY.—At Royal Society of Medicine, 5 p.m., St. Cyres Lecture of the Institute of Cardiology by Dr. Howard Burchell (Minnesota): Studies of Pulmonary Hypertension in Congenital Heart Disease.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—2 p.m., Professor C. P. Beattie: Toxoplasmosis.

Thursday, June 5

HILL END HOSPITAL MEDICAL SOCIETY.—8.45 p.m., Professor W. C. W. Nixon.
HONYMAN GILLESPIE LECTURE.—At Anatomy Theatre, University New Buildings, Edinburgh, 5 p.m., Dr. Thomas Anderson: Respiratory Infections in Early Childhood.
MANCHESTER MEDICAL SOCIETY: SECTION OF GENERAL PRACTICE.—At Cheadle Royal Hospital for Mental Diseases, 4.30 p.m., clinical demonstration of psychiatric cases by Dr. W. V. Wadsworth.
NUFFIELD ORTHOPAEDIC CENTRE.—At Wingfield-Morris Orthopaedic Hospital, 8.30 p.m., Dr. A. M. Cooke: A Physician Looks at Fractures.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Dr. R. Bodley Scott: Treatment of Leukaemia.

Friday, June 6

●INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. C. D. Calnan: clinical demonstration.
INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. J. G. Scadding: clinical demonstration.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—(1) 10 a.m., Mr. I. W. McPhee: Observations on the Genesis of Traumatic Shock. (2) 2 p.m., Sir James Learmonth: Biological Reserves in Man.
ST. MARY'S HOSPITAL MEDICAL SCHOOL.—At Wright-Fleming Institute Theatre, 5 p.m., Mr. Philip Rhodes: Prolapse of the Cord.
WHIPPS CROSS HOSPITAL MEDICAL SOCIETY.—At Langthorne Hospital, 8.30 p.m., Professor Clifford Wilson: Jaundice.

Saturday, June 7

●INSTITUTE OF OBSTETRICS AND GYNAECOLOGY.—At Hammersmith Hospital, 10 a.m., Professor I. Donald: Neonatal Respiratory Problems.

APPOINTMENTS

EAST ANGLIAN REGIONAL HOSPITAL BOARD.—K. Jones, L.R.C.P.&S.I., D.P.M., Assistant Psychiatrist, St. Andrew's Mental Hospital Group.
SOUTH-EASTERN REGIONAL HOSPITAL BOARD, SCOTLAND.—Eric Samuel, B.Sc., M.D., F.R.C.S., F.F.R., D.M.R.E., Head of the Department of Radiodiagnosis, Royal Infirmary, Edinburgh, and Adviser in Radiodiagnosis to the South-eastern Regional Hospital Board, Scotland; E. O. Lundholm, B.Sc., M.B., Ch.B., D.P.M., Psychiatrist (S.H.M.O.), East Lothian Mental Hospital, Haddington; Marjory A. Keith, M.D., F.R.C.P.Ed., Consultant Physician, Bruntsfield and Elsie Inglis Hospital, Edinburgh; R. F. Robertson, M.D., F.R.C.P.Ed., M.R.C.P., Consultant Physician, Deaconess and Longmore Hospitals, Edinburgh.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Burton.—On May 14, 1958, at 20, Sheen Gate Gardens, London, S.W., to Drs. Rosemary and John Burton, a daughter—Frances Ann.

DEATHS

Bremner.—On May 6, 1958, at Edinburgh, Frederick Russell Bremner, M.D., of Sandilands, Cupar, Fife.
Macleod.—On May 3, 1958, at Glen o' Dee Sanatorium, Banchory, Kincardineshire, John Farquhar Macleod, M.B., Ch.B., J.P., of Threave, Ramsay Road, Banchory, formerly of Eastleigh, Peterculter, Aberdeenshire, aged 77.
Matheson.—On May 6, 1958, at Sandwich, Kent, Farquhar Kenneth Matheson, M.B., Ch.B., aged 49.
Munro.—On May 8, 1958, at Glentworth, Buxton, Derbyshire, James Sutherland Munro, M.B., Ch.B.
Thomason.—On May 8, 1958, at his home, 67, Lodge Road, West Bromwich, Staffs, Reginald Thomason, M.B., Ch.B.

Any Questions ?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Medicines on Holiday

Q.—*What medical precautions and preparations would you advise for a family summer holiday in Brittany (including children aged 6 and 4)?*

A.—It is unwise to lay too much emphasis on the medical preparations for such a holiday. Most parts of Brittany are quite as safe as the average British holiday resort, and an attitude of extreme caution will only spoil the enjoyment. T.A.B. inoculations are unnecessary (they may be advisable for those who propose visiting Spain or southern Italy). Nevertheless, minor gastro-intestinal upset might occur during the first few days, and it would be reasonable to take a supply of mist. kaolin. and one of the non-absorbed sulphonamides. It is usually safe to drink piped water, but if there is any doubt about the origin or quality of the water there are plenty of pleasant alternatives readily available for children and adults. It would be wise to boil milk for the younger child, and a small stove which burns meta fuel is indispensable for this and many other purposes. Soft-skinned fruit and lettuce should be thoroughly washed before eating, and ice-cream should be brought only in shops or cafés.

It would be useful to make up a small first-aid kit before setting out. This might contain simple dressings, iodine, calamine lotion, and a reputable barrier cream against sunburn. In addition a bottle of aspirin, an antihistamine, and a preparation for motion sickness might be included. Oral penicillin is an excellent insurance against septic infections, but the increasing tendency to include the latest broad-spectrum antibiotic should be firmly resisted.

Diuretics

Q.—*What is the present range of diuretics and how do they work?*

A.—The older diuretics, such as potassium citrate, urea, and xanthine derivatives, such as aminophylline, are now little used. The choice rests between the following: (1) Mercurial diuretics—these act by inhibiting the tubular reabsorption of the chloride ion. The chloride ions carry sodium with them and to a less extent potassium, and the total volume of urine is increased with considerable electrolyte loss. The most widely used preparation is mersalyl, which must be given by intravenous or preferably by intramuscular injection. Mercaptopurine is another and less irritant mercurial diuretic which can be given subcutaneously. A recent orally administered preparation chlormerodrin may be used to keep patients who have been discharged from hospital free from oedema. (2) Acetazolamide acts as a diuretic by inhibiting the enzyme carbonic anhydrase and causing the excretion of an increased amount of bicarbonate. Hence a greater volume of water is excreted to maintain normal osmotic relationships. In practice this diuretic, which is given orally, has proved disappointing, since its effects are both relatively feeble and unpredictable. (3) Aminometradine and amisometradine are effective diuretics which can be given orally and act by diminishing the degree of absorption of sodium and chloride by the renal tubules. They are mainly of value in preventing the recurrence of oedema in a patient who has left hospital. Alimentary side-effects are said to be less common with the second and newer of these compounds. (4) Chlorothiazide causes an increase in the excretion of sodium, potassium, and chloride.[1 2] Thus it may lead to a mild hypokalaemic, hypochloraemic alkalosis. It is given orally and is both a quick and effective diuretic. It can be used in conjunction with mersalyl and may act when mersalyl is ineffective. (5) Digitalis acts as a diuretic in congestive cardiac failure through its action in improving cardiac and therefore renal function.

Mersalyl, with a wealth of clinical experience behind it, remains the diuretic of choice, but chlorothiazide, with its advantage of oral administration, may replace it if it proves to be as safe as initial experience suggests.

REFERENCES

[1] *Brit. med. J.*, 1957, **2**, 1355.
[2] Ibid., 1958, **1**, 990.

Senna and Colic

Q.—*Does syrup of senna tend to cause colicky pains when it is used as a laxative for babies?*

A.—Observation suggests that senna may produce colicky pains in some babies. It certainly may do so in women during the puerperium, and in a recent controlled clinical trial[1] 17% of those receiving relatively large doses of a standardized senna preparation complained of griping. The *B.P.* preparations of senna vary widely in the amount of active principle they contain, and some of the colic which occurs in babies may be due to excessive dosage. Standardized preparations given in the smallest dose which produces the desired effect would appear to be preferable.

REFERENCE

[1] Duncan, A. S., *Brit. med. J.*, 1957, **2**, 439.

Skin Staining and Varicose Vein Injection

Q.—*What treatment is there for deep-staining of the skin following varicose vein injection?*

A.—Pigmentation of the skin over the thrombosed vein is one of the complications of injection treatment and is one of the several reasons why it has been abandoned for the treatment of anything other than very small lengths of vein. An operation such as stripping, which is done through very small incisions, usually gives a much better cosmetic result as well as treating the disordered haemodynamics in a more efficient manner. The best treatment in a case like this is on conservative lines, as it is largely a matter of the cosmetic end-result, and any surgical interference would be likely to leave a scar. A course of physiotherapy with infra-red radiation to improve the blood supply combined with massage to increase the lymph drainage might help to remove the coloration. Pigmentation of the overlying skin is not uncommon after injection treatment and tends to improve spontaneously with time. However, if the skin is still "deeply stained" after six months it is unlikely that the discoloration will disappear completely.

Children's E.S.R.

Q.—*What is the normal erythrocyte sedimentation rate for children up to 14 years of age by both Wintrobe and Westergren methods?*

A.—The upper limit of the normal erythrocyte sedimentation rate for children up to the age of 14 years by the Wintrobe and Westergren methods is 15 mm./hr. Formerly the Wintrobe method was corrected for varying haematocrit by means of a correction curve proposed by Wintrobe and modified by Whitby and Hynes.[1] It has been increasingly realized, however, that correction may give a false impression of accuracy. Sedimentation of erythrocytes is governed by factors such as haematocrit, fibrinogen, and globulin concentration, which influence viscosity and rouleaux formation, and by the diameter of the tube. The degree of disease activity—that is, the amount of tissue destruction in inflammatory or neoplastic diseases—often correlates better with the uncorrected than with the corrected Wintrobe result, and in conditions with high viscosity and high haematocrit the tube diameter (2 mm.) limits sedimentation. The Westergren method seems to many people preferable

because of its better correlation with the inflammatory state. This is used without correction for haematocrit.

REFERENCE

1 Whitby, L. E. H., and Hynes, M., in *Disorders of the Blood*, 1953, 7th ed., edited by L. E. H. Whitby and C. J. C. Britton. Churchill, London.

Inheritance in Werdnig-Hoffmann's Disease

Q.—*Should parents who have lost three babies from infantile progressive muscular atrophy be advised not to have any more children?*

A.—Genetic factors in Werdnig-Hoffmann's disease have been investigated by Brandt.[1,2] The pattern of inheritance in his material indicated either a recessive trait or an incomplete dominance. The disease was self-limiting; it cannot be transmitted from one generation to the next. The evidence of genetic determination rests on the finding of multiple cases in one sibship and in pairs of identical twins. The rate of expression is clearly high in the family under consideration. It is possible that a fourth baby might be free of the disease, as Brandt's material shows, but one would give no further encouragement than this. Brandt's original work should be consulted.

REFERENCES

1 Brandt, S., *Amer. J. Dis. Child.*, 1949, **78**, 226.
2 —— *Werdnig-Hoffmann's Infantile Progressive Muscular Atrophy*, 1950, Munksgaard, Copenhagen.

Retinal Haemorrhage and Macular Degeneration

Q.—*Is there any treatment likely to hasten absorption and limit damage in a case of retinal haemorrhage?*

A.—There is no local treatment of proved value likely to hasten absorption and limit the damage in a case of retinal haemorrhage, apart from a reasonable amount of rest. Treatment should be directed towards the cause of the haemorrhage. Hormone treatment has not been found to be of benefit in senile macular degeneration.

Yoghourt or Milk?

Q.—*Is yoghourt preferable to milk in a reducing diet?*

A.—Yoghourt has about the same nutritive value as an equivalent amount of milk, except for the conversion of part of its lactose to lactic acid. In practice, however, taking yoghourt in place of milk may lead to a smaller consumption of food. The containers in which yoghourt is purchased tend to be smaller than for milk, and the price is higher. At home it is less easy to keep in plentiful supply than is milk. Moreover, its semi-solid consistency usually necessitates it being eaten with a spoon. A thirsty person can drink a glass of milk in a few seconds, but the spooning up of the same amount of yoghourt will be a more lengthy procedure. Should an individual liking for yoghourt outweigh the effect of these limitations, however, there seems no reason why excess of yoghourt should not contribute to adiposity.

Antibiotics in Diverticulitis

Q.—*What place have antibiotics in the management of diverticulitis, particularly in the elderly where operation may be contraindicated?*

A.—Antibiotics are invaluable in the management of diverticulitis. It is probably best to give penicillin and streptomycin parenterally, as the inflammation extends well away from the lumen of the bowel. A short course of five days with 500,000 units penicillin and 0.5 g. streptomycin twice daily will usually abate an acute attack. Alternatively, tetracycline 0.5 g. four times daily for five days may be given. In practice the insoluble sulphonamides like sulphaguanidine and sulphathaladine are disappointing, as it is not sufficient to sterilize the bowel when the inflammation extends outside the bowel.

NOTES AND COMMENTS

Poliomyelitis Vaccination of Close Contacts.—Dr. W. H. CRICHTON (Holt, Norfolk) writes: In reply to a question on this subject ("Any Questions?" May 3, p. 1077) you have stated that it is advisable to immunize young contacts of a case of poliomyelitis on the grounds that the development of natural immunity cannot be assumed in every case and that ". . . if they are already immune, further immunization will do no harm." Present belief appears to be contrary to this view for the following reasons: (1) that the development of antibody response to poliomyelitis vaccination is not immediate and therefore unlikely to be effective in checking spread among close family contacts; and further (2) that during the stage of viraemia, which may reasonably be expected among contacts in such circumstances, there is an actual risk of provoking an attack of poliomyelitis by an injection which might "attract the virus from the blood stream into overactive nerve cells with resulting paralysis of muscles" (*Journal*, August 31, 1957, p. 513). On this account the vaccination of close contacts has not been practised. Indeed, it has been studiously avoided, and I may add that hitherto in no case have any "secondary" cases been experienced among close contacts. In these circumstances an authoritative clarification of the matter would be appreciated. Clearly, if the views expressed in "Any Questions?" are upheld, the poliomyelitis vaccination of close contacts should become an important routine measure in the control of the disease. On the other hand, if the contrary views expressed last year prevail, there would appear to be no justification for such a step to be taken and a not inconsiderable degree of risk.

OUR EXPERT replies: In answering the question on the subject of poliomyelitis vaccination of close contacts I had the long-term solution to the problem in mind, rather than any immediate action. Clearly active immunization at this stage could hardly be expected to confer protection. As Dr. Crichton rightly points out, the time factor alone, with the inevitable delay that must ensue before active immunity develops, makes vaccination at this stage impracticable. Further, the risk of provoking paralysis has to be considered, although there is little evidence that poliomyelitis vaccines have a provocative effect. It seemed from this question, and from several others on the same subject, that the questioner was more concerned with the future. Should these contacts be considered immune or non-immune? In all probability brother and sister contacts will have become infected, but it cannot be taken for granted, as it depends on so many factors. Therefore it seems safer to assume that such contacts are still non-immune. Consequently no change in the current practice of avoiding immediate immunization of close contacts is envisaged, but it should subsequently be carried out if protection is to be assured. The occurrence of multiple infections within families is now well recognized. Such cases represent secondary cases among contacts, although it is frequently difficult to identify the primary case, as they are so often asymptomatic. The events that followed the use of certain batches of vaccine in the U.S.A. in 1955 may be mentioned in this connexion. 74 cases of paralysis developed among vaccinated children. Subsequently 104 cases were reported among family contacts and a little later some 20 cases were encountered among community contacts.

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